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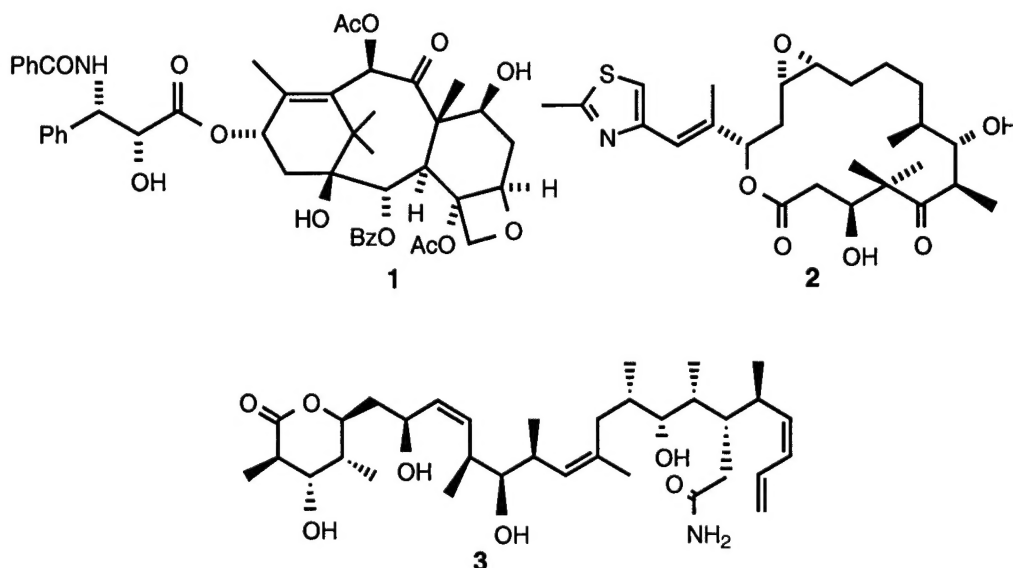
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13. ABSTRACT (Maximum 200 Words) This project is directed towards the design and synthesis of new drugs to treat breast cancer. Several naturally occurring substances have recently been discovered that have the same biological activity as the very important anticancer drug Taxol. We are using both computational and synthetic approaches to determine the parts of these very different compounds that are important for their biological activity. The determination of these "critical parts" could lead to the development of simpler structures that could be very powerful anticancer drugs. During the grant award period, we have prepared new structures based on the taxol-like substance epothilone. While the structures of the new compounds that we have prepared are very much like epothilone itself, we have not yet been able to prepare a simple structure with the same anticancer properties as taxol and epothilone.				
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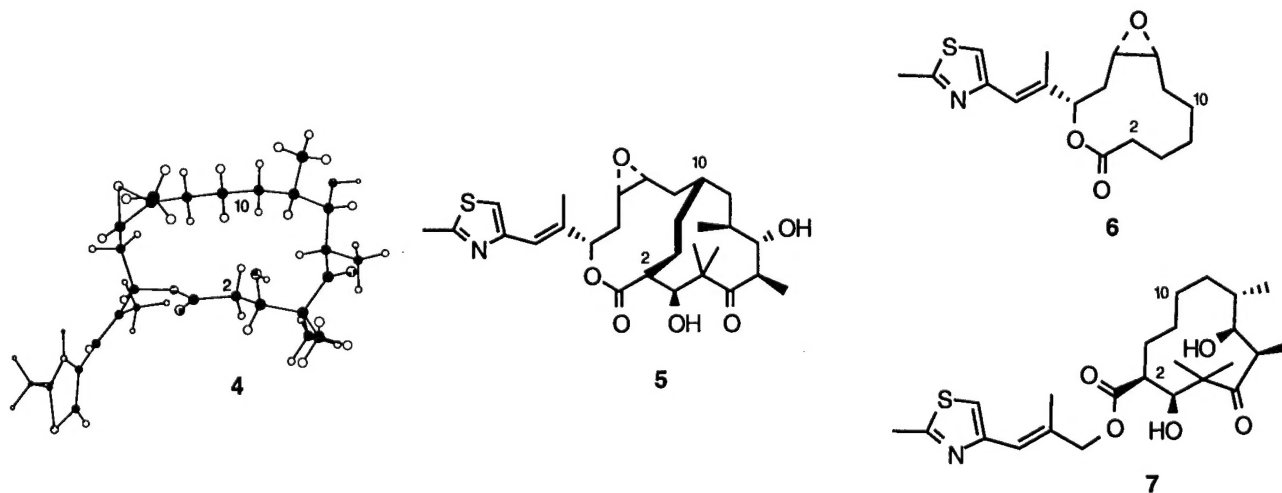
INTRODUCTION

This project is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™, **1**. Several new natural products, i.e., epothilone **2** and discodermolide, **3**, have recently been discovered that operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization. This family of microtubule-stabilizing compounds affords a unique opportunity for a collaborative approach using synthetic and computational studies for the elucidation of the pharmacophore common to these structurally dissimilar substances. Such an advance could lead to the development of a novel family of breast cancer chemotherapeutics.



BODY

Significant progress has been achieved in realizing the first five tasks in the approved Statement of Work.



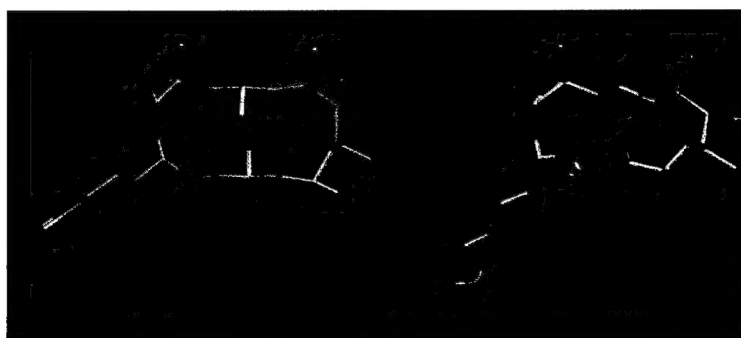
Task 1. The synthesis of both left- and right-hand halves of epothilone 1 has been achieved.

There were several factors that needed to be considered in the design of the new bridged bicyclic epothilone analog **5**. First, any constraints that were introduced to the system would have to be innocuous. We didn't want to introduce anything into the epothilone system which could, on its own, perturb the system such that it would interfere with binding of the molecule to β -tubulin. Second, we didn't want to add anything to the molecule which would significantly affect the hydrophobicity or hydrophilicity of any region of the molecule, as this could certainly alter its binding profile. Finally, the purpose of any introduced constraint would be to fix the important moieties of the molecule in this one defined conformation, the X-ray conformation.

Using CHARMM and Quanta for molecular modeling, we were able to discover a new compound which fit the above criteria.¹ The novel epothilone analog **5**, differs from the natural product in that we have introduced a two carbon transannular tether from C2 to C10. This tether would rigidify the epothilone macrocycle.

Single point energy minimizations of **5** using CHARMM as our force field, produced a minimized form of **5**. The minimized conformation of **5** is shown on the left side of Figure 1 below. Examination of this new compound showed that, as we had hoped, introduction of this two carbon transannular tether did not perturb either the top or the bottom face of the epothilone molecule. Hence, we reasoned that the introduction of these two additional methylene units to the epothilone molecule should not interfere with its binding. Comparison of the minimized form of **5** to the epothilone X-ray conformation showed us that introduction of the two-carbon bridge to the epothilone skeleton also succeeded in "freezing out" the X-ray conformation of the molecule. As shown on the right of Figure 1, an overlap of the minimized form of analog **5** (shown in blue) with the epothilone X-ray conformation (shown in gray) showed excellent conformational agreement around the periphery of the macrocycle. In particular, we were interested in the integrity of the conformation around the C3 through C8 region of the molecule, as this acyl region had been shown to be particularly sensitive to perturbations. As the figure shows, agreement between **5** and the natural product in this region of the molecule was remarkable. We weren't concerned by the positional disagreement of the two sidechains in this overlap, as we believed that this region of the molecule possessed adequate degrees of freedom such that the requisite conformation could be achieved. Because this bridged compound is "locked" in the same conformation as the epothilone X-ray without introducing any significant perturbation to the system, if such an analog maintained biological activity, we believed that would support our hypothesis that the active conformation of epothilone is that of the X-ray conformation.

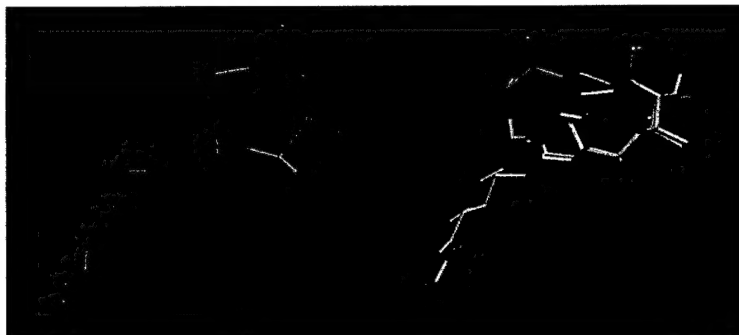
Figure 1



In keeping with the goal of this project, we believed that the left and right-hand halves **6** and **7** would be most interesting and noteworthy if they maintained the epothilone X-ray conformation of the individual hemispheres. Independent modeling of these analogs using CHARMM and Quanta showed that

each overlay well with the appropriate region of the original epothilone X-ray conformation. The left side of Figure 2 below shows the minimized form of the eastern hemisphere analog **7**. The overlap of this analog (shown in yellow) with the epothilone X-ray conformation (shown in gray) is shown on the right of the figure. The modeling showed excellent overlap in the C3 through C8 region of the molecule, the "hot spot" of epothilone. Again, we weren't concerned with overlap of the sidechain since its conformational flexibility should allow it to adopt whatever conformation would be necessary for binding.

Figure 2



The minimized conformation of the western hemisphere analog, **6**, is shown on the left of Figure 3 below. The overlap of this analog (shown in green) with the epothilone X-ray conformation (shown in gray) is illustrated on the right of Figure 3. Although the regions of the epothilone molecule encompassed by this western hemisphere analog have been shown to be rather tolerant to modification, it was important that analog **6** maintained the integrity of the conformation about the periphery of the macrocycle. Figure 3 shows that, in fact, this analog accomplished this task.

Figure 3

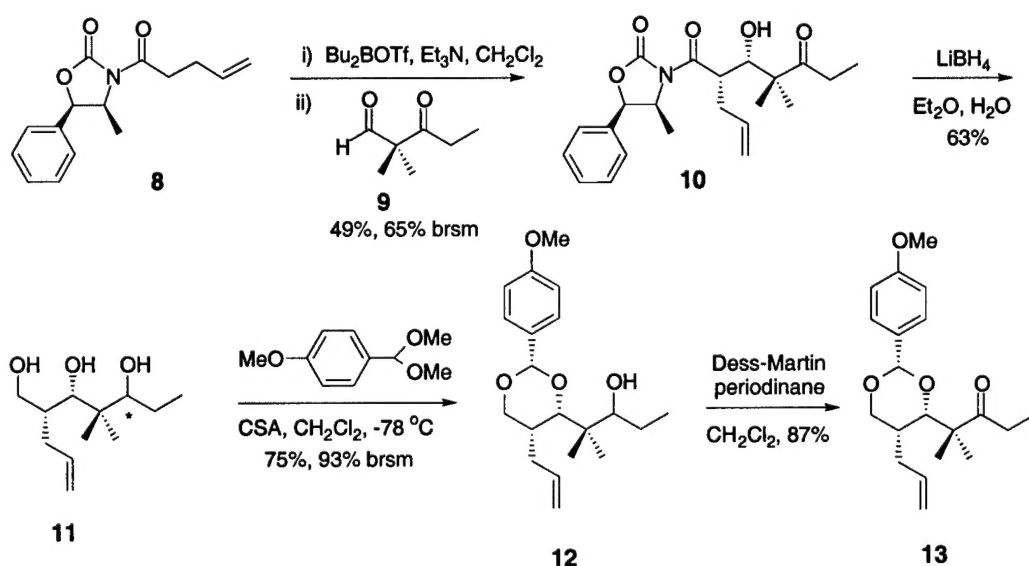


It was at this stage in the development of this project that we were faced with a serious strategy decision. We had, at this point, designed three very exciting novel analogs of epothilone, and we needed to decide on which we were going to focus our synthetic efforts. While the original constrained analog **5** was the basis of our initial hypothesis, it was tempting to sidetrack onto the synthesis of the individual hemispheres of the epothilone molecule. In particular, the eastern hemisphere analog was extremely enticing. This analog possessed all of the functionality of the natural product which was known to be essential for biological activity: it contained the entire "hot spot" region of the molecule as well as the entire aromatic sidechain. In addition, our modeling calculations suggested that **7** maintained the integrity of the epothilone X-ray conformation in the "hot spot" region of the molecule. If this was, in fact, the active conformation of the molecule, we would be creating an analog which provided the known necessary

functionalities in the known necessary conformation. The synthesis of these novel structures is outlined in Scheme 1.

We investigated the use of the non-protected keto-aldehyde **9** (Scheme 1).² We hoped that removal of the ketal functionality would minimize steric issues, thus improving the yield of the aldol reaction. We reasoned that reductive removal of the chiral auxiliary from **10** would concomitantly reduce the ketone, thus skirting the problem of cyclization of the free primary hydroxyl onto that center. We would be left with the task of differentiating the three resulting hydroxyl groups of **11**. Our initial thoughts were that this could be accomplished most effectively by tying the primary hydroxyl -- which we rationalized could be selectively protected in the presence of the secondary hydroxyls -- to its neighboring secondary hydroxyl via a cyclic acetal. This would leave the distal secondary hydroxyl to be oxidized to the desired ethyl ketone.

Scheme 1

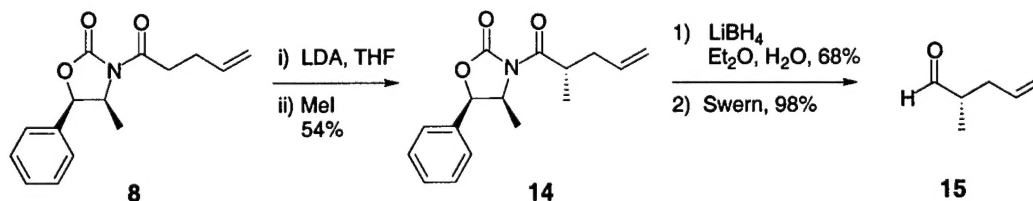


As is shown in Scheme 2 below, we were immediately encouraged by the aldol reaction between **8** and **9**, as it gave a 25% increase in yield over previous aldol results. Presumably, this improved yield can be attributed to the decrease in steric hindrance about the aldehyde center. Next, reductive removal of the chiral auxiliary with concomitant reduction of the ketone provided triol **11** as a mixture of diastereomers (at the indicated center). A variety of protecting groups and conditions were investigated for the protection of triol **11**. We finally discovered that treatment of **11** with anisaldehyde dimethylacetal and catalytic camphorsulfonic acid in methylene chloride at -78°C on small scale provided exclusive formation of the desired regioisomer **12** as a single diastereomer. The specific stereochemistry of the newly-formed stereocenter was never conclusively established, however, the phenyl group would presumably adopt an equatorial orientation on the six-membered ring, translating to an α -substituent as shown. It should be noted that the same reagents at room temperature gave solely the undesired internal cyclic acetal regioisomer, the thermodynamic product of the reaction. With these two hydroxyls now protected, the remaining secondary hydroxyl was oxidized using Dess-Martin periodinane¹¹ to afford the desired ethyl ketone subtarget **13**.

With ethyl ketone **13** in hand, we now needed aldehyde **15** for coupling via an aldol reaction. The synthesis of aldehyde **15** was accomplished from the common intermediate **8** (which was also used in the

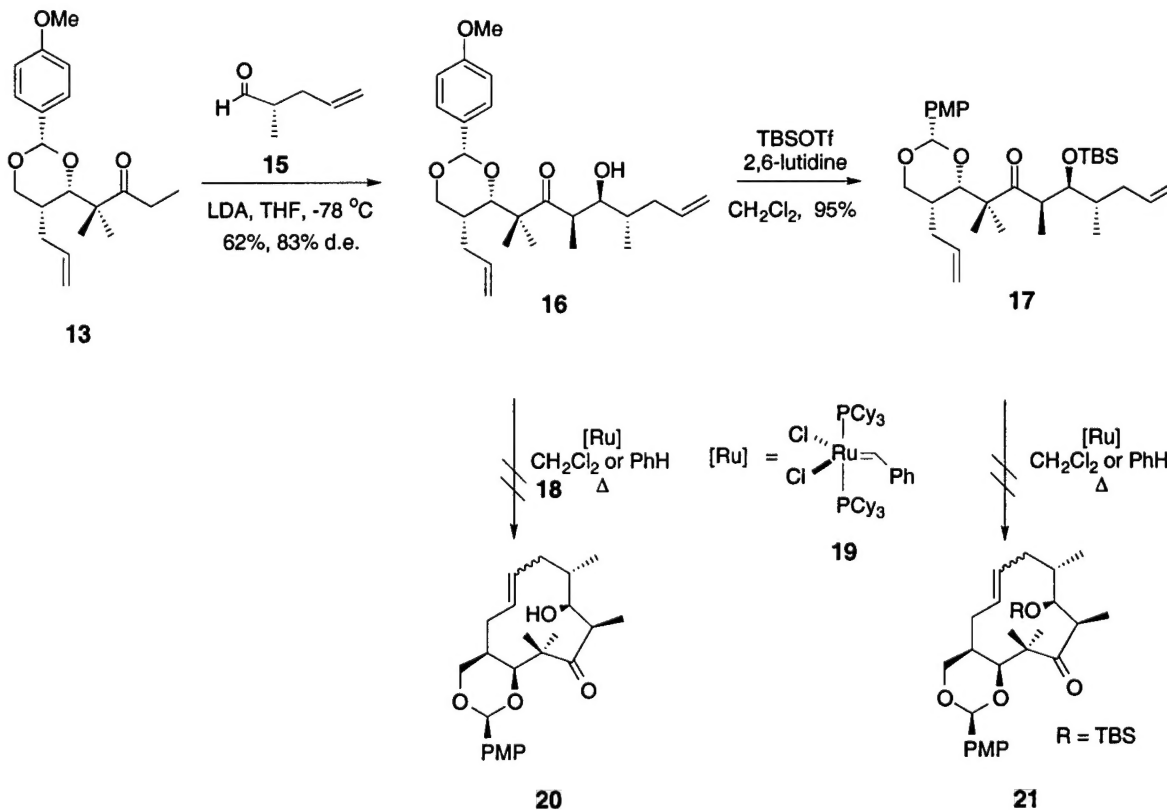
preparation of ethyl ketone **13**), as shown in Scheme 2. Diastereoselective methylation was accomplished with LDA and methyl iodide to give **14**. The chiral auxiliary was then reductively removed using LiBH_4 in ether/water. Oxidation of the resulting alcohol under Swern conditions provided the desired aldehyde **15**.¹³ Aldehyde **15** was formed in nearly quantitative yield, only if extreme care was taken in this oxidation and the subsequent purification, as this aldehyde was exceedingly volatile.

Scheme 2



As is shown in Scheme 3 below, the aldol reaction between ketone **13** and aldehyde **15** was performed under the same conditions as were used by Schinzer (-78°C using LDA in THF). We were delighted to observe that the selectivity in our reaction was 11:1. The major diastereomer was formed in 62% yield and 83% diastereomeric excess and was assigned the stereochemistry shown for **16** based on the literature precedent. This stereochemistry was later confirmed by an X-ray crystal structure of a crystalline descendent.

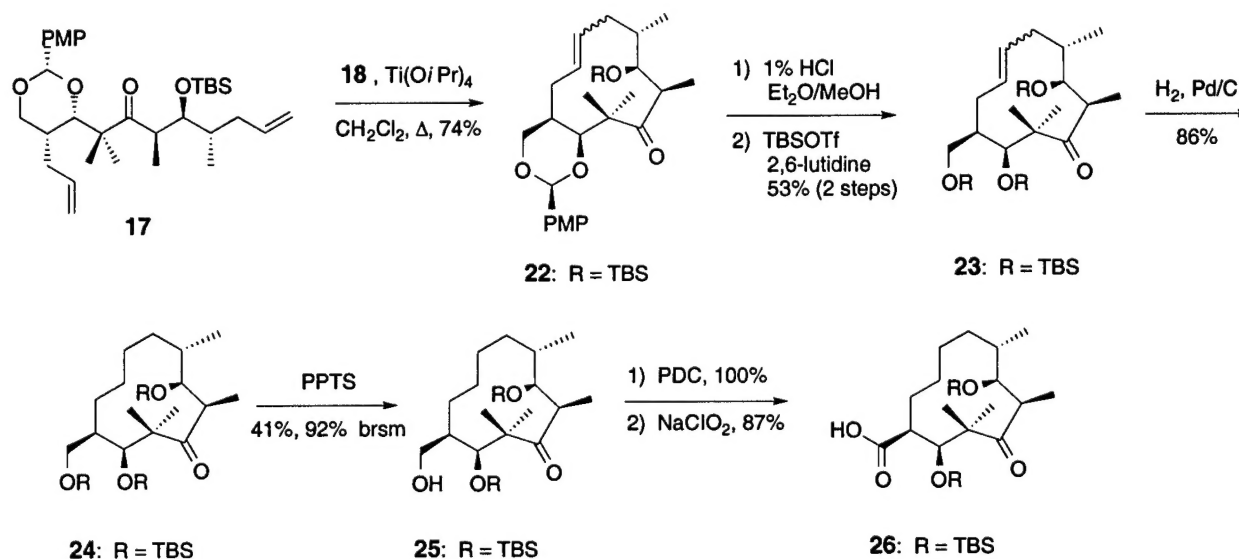
Scheme 3



Having now prepared aldol adduct **16**, the next step in our synthetic sequence was the cyclization of this bis-terminal olefin to obtain the eleven-membered ring. Initial metathesis attempts on the free hydroxyl substrate **16**, using Grubbs' catalyst,³ **18** in benzene (room temperature or 50°C) or methylene chloride (room temperature or reflux) were met with failure, as is illustrated in Scheme 3. In order to produce an additional substrate on which to attempt the metathesis reaction, the free hydroxyl of **16** was treated with TBSOTf and 2,6-lutidine to protect the alcohol as its corresponding TBS ether, **17**.

The protection of **17** affected significant and interesting changes in the proton nuclear magnetic resonance (NMR) spectrum. In addition to the expected chemical shift differences for the methine proton on the carbon bearing the now protected alcohol functionality, an interesting change was noted in the vinyl region of the proton spectrum. Whereas in the spectrum of the bare hydroxyl diene **16** the resonances of the two chemically different internal vinyl hydrogens coincided, and the four chemically different terminal vinyl hydrogens coincided, shifts of these hydrogens were noted upon TBS protection. The chemically different vinyl protons were no longer coinciding but were giving rise to separate resonances. As we normally would not expect such a chemical shift change at regions of a molecule so distant from the point of protection, this change suggested that a significant conformational change in the molecule was being affected by this simple TBS protection.

Scheme 4

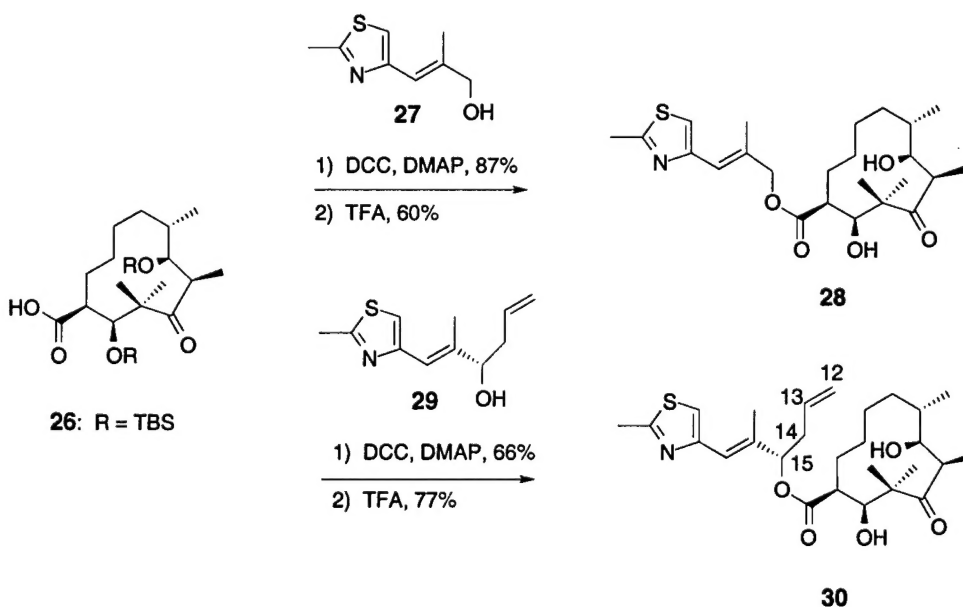


One possible explanation for this conformational change was that protection could have disrupted a conformationally restricting hydrogen bond. Some additional data which supported this hypothesis was found upon examining the IR spectra of these two compounds. The carbonyl stretching frequency for **16** was seen at 1680 cm^{-1} . This value was quite low for an α - β saturated ketone, but would be easily rationalized if the carbonyl were participating in a strong hydrogen bond interaction (thereby lengthening the carbon-oxygen bond length and lowering its observed stretching frequency). Upon protection of the hydroxyl, the carbonyl stretching frequency for **17** was observed at 1695 cm^{-1} . We anticipated that different reactivity of the protected molecule **17** would be observed (in the metathesis reaction) since the molecule was adopting a different conformation. Unfortunately, as is shown in Scheme 3, **17** also failed to produce the desired cyclized product under the metathesis reaction conditions described above. Instead, treatment of **17** with Grubbs' catalyst **18** resulted only in recovered starting material.

As is shown in Scheme 4 below, subjection of TBS ether **17** to Grubbs' ruthenium catalyst **18**, in refluxing methylene chloride with 0.3 equivalents of titanium tetrakisopropoxide provided the desired cycloundecene **22** in good yield, as a 1.9:1 ratio of cis to trans alkenes ($J = 10.8$ Hz for cis (major); $J = 15.1$ Hz for trans (minor)). The success of this reaction was dependent on high dilution conditions (0.2 mM); more concentrated conditions resulted in significant amounts of dimerization at the cost of cyclization.

The success of this reaction was particularly noteworthy in that it was the first reported example of the application of ring-closing olefin metathesis methodology to the synthesis of an eleven-membered ring.⁴ Incidentally, the same conditions which were successful for the cyclization of **17** were attempted with the free hydroxyl bis-terminal olefin **16**, but reaction did not occur. The failure of this bare hydroxyl substrate to metathesize is presumably due to the conformational constraints imparted by the hypothesized hydrogen bond discussed above.

Scheme 5



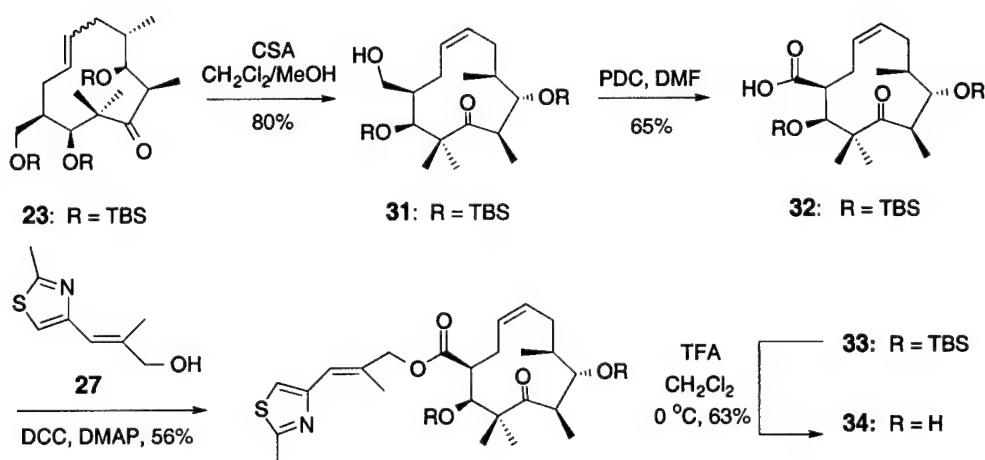
On the heels of the success of the metathesis reaction, all that remained in the synthesis of the eastern hemisphere analog of epothilone were minor functional group manipulations. To that end, hydrolysis of the benzylidene acetal of **22** (an inseparable mixture of olefin isomers) under acidic conditions provided a diol which was disilylated using TBSOTf and 2,6-lutidine to give trisilyl ether **23** (Scheme 4). Next, hydrogenation of the mixture of cis and trans olefins provided the saturated eleven-membered ring **24**. Selective deprotection of the primary TBS group in the presence of the two secondary TBS ethers was then accomplished using PPTS. This provided primary alcohol **25** in a modest 41% yield, but with 92% yield based on recovered starting material. This alcohol was oxidized in two steps, with 87% overall yield, to the corresponding acid **26**.

Scheme 5 shows the final steps toward the synthesis of our target compound. Acid **26** was coupled to the known thiazole side chain **27**⁵ using 1,3-dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) and the two remaining silyl protecting groups removed with TFA to give the desired eastern hemisphere analog **28**. We then prepared an additional eastern hemisphere analog of epothilone, **30**, by coupling to the known thiazole side chain **29** followed by deprotection of the two TBS

protecting groups. The rationale for the preparation of **30** as an additional analog was that it incorporated the C12-C14 carbons of epothilone with the natural stereochemistry at C15. As this analog more closely mimicked the natural product (in molecular formula), we speculated that we had reproduced the hydrophobicity (and therefore solubility) of the natural product.

Our synthetic sequence afforded us the opportunity of preparing an additional analog, as is shown in Scheme 6. When trisilyl ether **23** was deprotected using camphorsulfonic acid in methylene chloride and methanol, selective monodeprotection of only one of the double bond isomers was observed. This isomer was separated from the other components of the mixture and was carried through the sequence outlined in Scheme 6 to produce analog **34**. The olefins in Scheme 6 were assigned *cis* stereochemistry based on the vinyl proton coupling constant of 10.7 Hz. The synthesis continued with oxidation of the primary alcohol in **31** to its corresponding acid in one step (using PDC) to provide **32**. Coupling with the thiazole sidechain **27** provided ester **33**. The silyl protecting groups were then removed to give our third eastern hemisphere analog **34**. Molecular modeling analysis of **34** showed that this unsaturated analog overlaid well with the appropriate portion of the epothilone X-ray conformation.

Scheme 6



Task 3. Biological Evaluation of Epolithilone Analogs

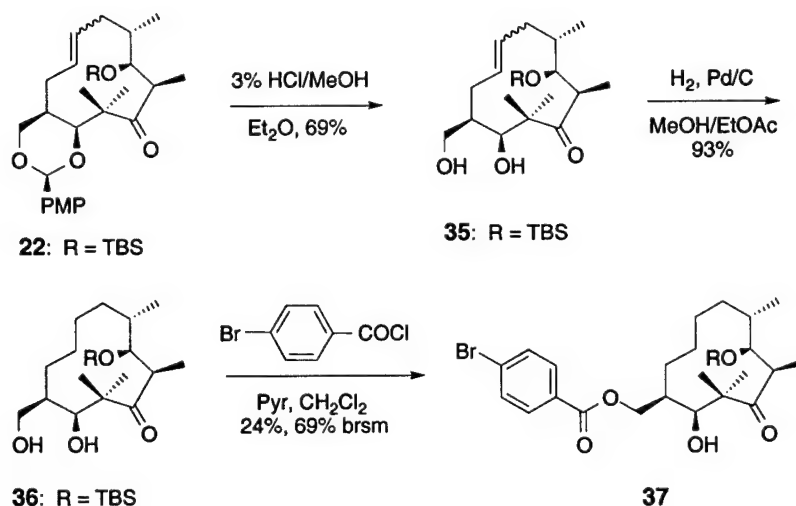
Analogs **28**, **30** and **34** were sent to Dr. Susan Horwitz at the Department of Molecular Pharmacology at the Albert Einstein College of Medicine for biological evaluation. In addition, the western hemisphere of epothilone, **6** was sent for evaluation. All of the analogs were screened in tubulin turbidity measurement experiments and tubulin depolymerization experiments, which are standard assays for the discovery of compounds which operate by the same mechanism of action as paclitaxel. Unfortunately, none of these compounds displayed activity in these assays. The lack of activity for the western hemisphere analog **6** was not surprising, as it did not contain the "hot spot" region of the molecule (C2 through C8) which had been shown to be essential for maintaining biological activity. However, the lack of activity of the eastern hemisphere analogs was quite surprising to us. The eastern hemisphere analogs contained the entire "hot spot" region of the molecule as well as the aromatic sidechain, the two elements of epothilone which have been shown to be important for inducing the desired biological response. In addition, the eastern hemisphere analog **34** contained the same number of carbons present in the natural product and possessed the natural stereochemistry at C15. Consequently, we speculated that this analog would mimic epothilone's solubility; we could therefore rule out solubility factors as an explanation for the lack of activity seen in these analogs. What did this lack of activity mean then? In order to be able to draw

any conclusion from these results, we needed to be able to first determine whether or not we had succeeded in our first goal -- to mimic the natural conformation of the "hot spot" region of the epothilone molecule.

Task 2. Molecular Modeling of Epothilone Analogs

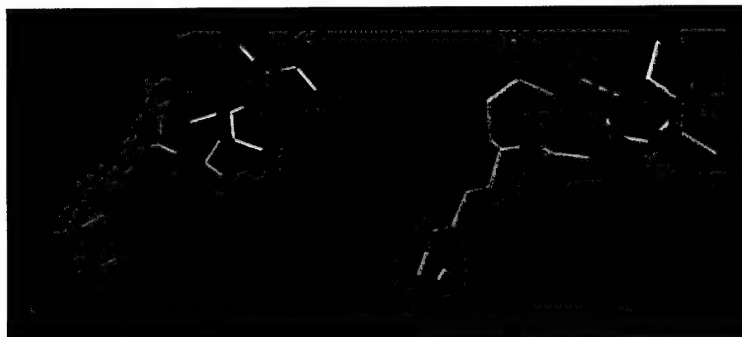
To begin our scrutinization of these eastern hemisphere analogs, we set out to prepare a crystalline derivative of the eleven-membered ring. Although we had been quite confident of the integrity of the stereochemical relationships in our analogs, the examination of a crystalline derivative would allow us to absolutely confirm these relationships as well as to examine the conformation about the eleven-membered ring. To this end, the benzylidene acetal moiety of **22** was hydrolyzed under acidic conditions to provide the diol **35**, as in Scheme 7 below. Hydrogenation of the mixture of olefin isomers then provided the saturated eleven-membered ring **36**. Treatment of this diol with excess *para*-bromobenzoylchloride provided a solid derivative **37**, which was crystallized via slow evaporation of diethyl ether at -5 °C. This process provided crystals suitable for X-ray analysis and the crystal structure was solved by Dr. Pat Carroll confirming the structure and stereochemistry.

Scheme 7



Having acquired the crystal structure, we were also afforded the opportunity of examining the conformation of this eastern hemisphere derivative with respect to the overlap of the 11-membered ring with the corresponding region of the epothilone molecule. The X-ray crystal structure of **37** is shown in its three dimensional representation on the left of Figure 4 below. The overlap of this derivative with the epothilone X-ray conformation is shown on the right of this figure, where the epothilone molecule is shown in gray and the crystalline derivative **37** is shown in orange. The *para*-bromobenzoyl group and the TBS ether have been deleted from the orange structure for simplicity. What one can easily discern from this figure is that we had not accomplished what we set out to do. The conformation of our analog does not correspond well with that of the natural product in the crucial "hot spot" region of the molecule. By creating a molecule whose conformation so greatly differs from epothilone's conformation in a region of the molecule which has been shown to be so sensitive to any minor perturbation, we have introduced a variable which, on its own, could be responsible for the lack of biological activity observed for this analog. In other words, without having mimicked the conformation of the "hot spot" region of the molecule, we could not yet make any conclusive comment regarding the viability of the eastern hemisphere of epothilone on its own.

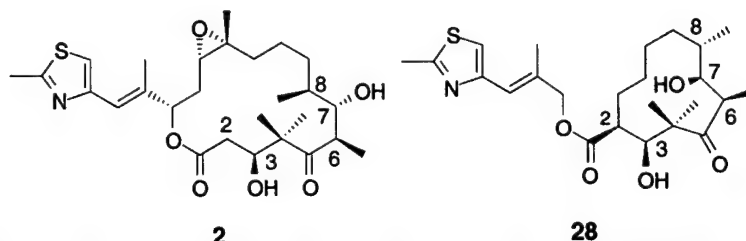
Figure 4



There remained, however, the possibility that the TBS protecting group on **37**, with its steric bulk, was perturbing the conformation of **37** in a way that our final eastern hemisphere analog **34** would not experience. Consequently, we felt it was possible that our final analog **34** could be adopting the desired conformation. In order to examine the conformation of **34** we chose to use proton NMR spectroscopy. Since the Karplus relationship correlates coupling constants to bond angles, we could compare coupling constants for analog **34** and epothilone as a means of comparing conformations.⁶ Similar coupling constants could be translated into similar bond angles and hence similar conformations. However, since our analog had an additional substituent at the C2 position when compared to the natural product, and since differing substituents can alter coupling constants regardless of dihedral angle,⁷ we did need to be mindful that a small discrepancy in coupling constant for C2 could merely be a result of the structural difference at this position.

As the solution and X-ray conformations of epothilone are believed to be one in the same, by comparing the conformation of **28** to the solution conformation of epothilone, we were also comparing it to the X-ray conformation of the natural product.⁸ Specifically, we could compare the coupling constants observed for the C2 through C8 regions of both compounds. Table 1 below shows a comparison of the coupling constants observed for the "hot spot" region of epothilone B, **2**, to those found for the same region of the eastern hemisphere analog, **28**. The coupling constants for epothilone were reported by the Georg group in 75% DMSO/25% D₂O,⁹ therefore our spectrum was recorded in that solvent system as well. What we discovered by comparing the two spectra was that the 2, 3 coupling constant for our analog differed significantly from that of epothilone. Our analog had only one proton at the C2 position, and molecular modeling analysis of the two compounds' three dimensional structures showed that the 2 proton in **28** corresponded to the 2b proton of epothilone. Consequently, we would expect the 2 proton of **28** to have a similar coupling to the 3 proton as the 2b proton in epothilone, if the two molecules were adopting the same conformation in this region of the molecule. Unfortunately, while our 2, 3 coupling constant was 6.5 Hz, the value reported for the epothilone molecule was 3.0 Hz. As mentioned above, we needed to consider whether or not this difference was due to the additional C2 substituent on our analog. A shift to a larger coupling constant is not what one would expect by adding an additional carbon substituent to the C2 position, however, so we felt we could rule this factor out as a reason for the difference. Despite the 2, 3 discrepancy, we saw very good agreement in the C6-C8 region of the molecule. With the 6, 7 proton coupling constant for epothilone being 9.0 Hz, we saw a 10.0 Hz coupling constant, a difference within an acceptable margin of error. Again, we saw good agreement with the 7, 8 coupling constant for the natural product, with the reported value being less than 1.0 Hz and our value also being less than 1.0 Hz. Unfortunately, mimicking the conformation in only one half of the "hot spot" region of this molecule was not good enough. We felt that this discrepancy, in conjunction with the poor overlap of our crystalline derivative **37** (as shown in Figure 4), warranted a close re-examination of the molecular modeling portion of this project.

Table 1



Coupling Protons	<i>J</i> (Hz)	<i>J</i> (Hz)
2a, 3	11.0	----
2b, 3	3.0	6.5
6, 7	9.0	10.0
7, 8	< 1.0	< 1.0

At this point, we began an in-depth inquiry into the molecular modeling portion of this project. Up until this point, we had been performing our molecular modeling using CHARMM and Quanta, programs introduced to us by Dr. Paul Axelsen in the Department of Pharmacology at the University of Pennsylvania. The modeling had consisted of simple equilibration and minimization cycles of structures imported into the program. These modeling techniques provided us only with one minimized structure per imported structure, a structure which reflected the local minimum of energy closest to the starting imported structure. After discussing this method of modeling with several experts in the field, it became clear that a method of modeling in which multi-step conformational searches were performed was needed. To this end, we began a detailed study of the epothilone molecule and our analogs using MacroModel as a tool for performing Monte Carlo conformational searches with the MM2* force field.¹⁰ The number of steps needed for an exhaustive conformational search for each molecule was determined by running several searches and increasing the number of steps performed in each until 1) no new structures were being produced (to ensure that we had high probability of having found the global minimum), and 2) the global minimum had been found several times. The results of these modeling experiments provided a collection of low energy conformations (ranked in order of energy) for each imported structure, and the resulting conformations were manually classified into families.¹¹

These new modeling experiments showed, categorically, that the previous modeling techniques which had been employed (i.e. using CHARMM in Quanta for single point energy minimizations) had been completely unsatisfactory for determining the likely conformations of these molecules. The specific outcome of these searches will be discussed in detail in the next chapter. Results of the conformational searches on the epothilone molecule itself showed that the application of molecular modeling to this system was a very difficult task, as several low lying energy conformations were produced for this macrocycle. Comparison of the known X-ray conformation of the molecule with all of the conformational families predicted by MacroModel showed that the X-ray conformation did not fall into any of the lowest energy families, but instead lay about 3 kcal/mol higher in energy than the lowest energy conformation. After discussing this anomaly with Dr. Clark Still, who had designed MacroModel, he informed us that he had also attempted applying these molecular modeling techniques to the epothilone molecule and had also found the unusual result of the mismatch of the computer-generated structures and the existing X-ray conformation.

With these issues in mind, we expanded our modeling analysis to the eastern hemisphere analogs and performed Monte Carlo conformational searches on these compounds. Again, several low lying conformations were produced, and these structures were classified into conformational families.¹² Scrutiny of the families of conformations produced showed that the conformation of the eleven-membered ring eastern hemisphere analog which overlaid best with the X-ray conformation of the natural product was not the lowest conformation available to this analog. There were several families of conformations which were lower in energy that did not overlay well with the eastern hemisphere of the natural product.¹³

By having so many low energy conformations available to this eleven-membered ring eastern hemisphere analog, we had no reason to be confident in saying that this analog would have any probability of existing in the desired conformation. More simply stated, we had not accomplished what we had set out to do -- *we had not developed an eastern hemisphere analog of epothilone which mimicked the X-ray conformation of the natural product.*

Task 4. Second Generation Design and Synthesis

In conclusion, we modified our molecular modeling techniques such that we now were using Monte Carlo conformational searches in MacroModel for the examination of our novel analogs. After discovering that this was the method of choice for this type of modeling investigation, it seemed prudent to reinvestigate our original bridged analog **5**. Conformational searches on the bridged analog **5** using our new methods suggested, however, that the low energy conformations available to this analog did not possess the conformation we had hoped for. Figure 5 below shows one of the lowest energy conformations available to this bridged analog on the left and the corresponding view of the epothilone X-ray conformation on the right. What is easily noticed from the figure is that introduction of the saturated ethylene spacer into the epothilone macrocycle affected a pucker in the ring, sticking the bridge up and out of the macrocycle instead of remaining in the plane of the macrocycle as we had originally aspired to when we designed this analog. When comparing this conformation with the epothilone X-ray conformation we notice that this bridge perturbs the top face (as shown) of the molecule. This perturbation to the system was unacceptable, as it could possibly be offensive to the binding sight, thus preventing docking of the molecule.

Figure 5

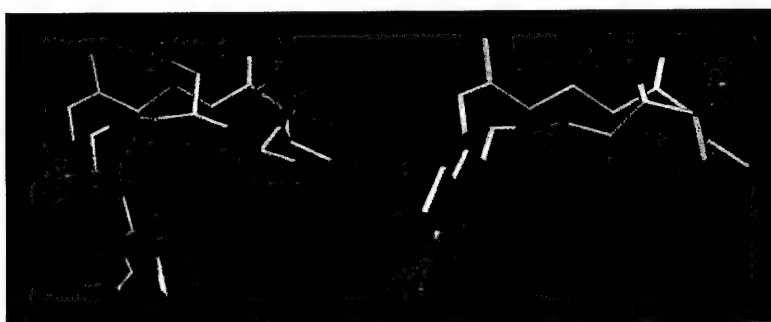


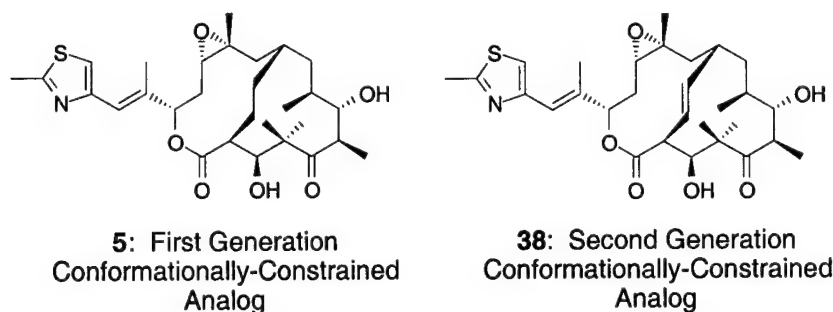
Figure 6 shows the overlap of the lowest energy conformation available to **5** in red and the epothilone X-ray conformation in white. Analysis of the "hot spot" regions of the molecules, in particular, shows significant discrepancy between the desired conformation and the conformation of **5**. The constraint built into **5** (the saturated two carbon tether) was not creating the desired conformational restrictions. Similar analysis of all of the low energy conformations available to **5** showed that none of them had satisfactory overlap with the epothilone X-ray conformation.

Figure 6



It seemed that the most logical and effective way of rectifying the problem with analog **5** would be to introduce an unsaturation into the bridge, specifically in the form of a trans alkene, **38**. By having a rotationally restricted trans alkene connecting C2 to C10, the bridge would not have the luxury of puckering up and out of the macrocycle. We reasoned that the bridge would then be fixed in the plane of the ring, as desired. Figure 38 shows the second generation "conformationally-restricted" epothilone analog.

Figure 7



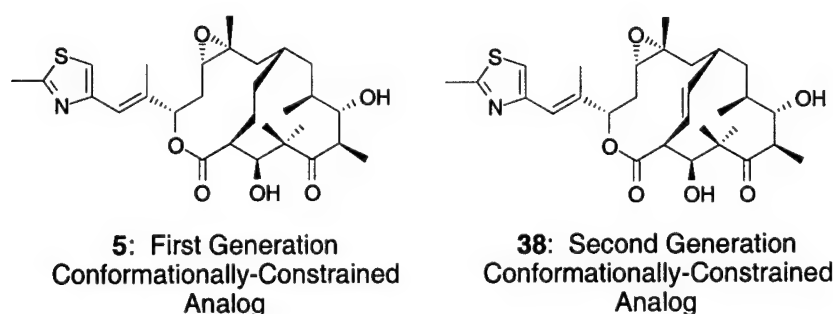
Conformational searches on **38** showed that this unsaturation, in fact, did serve to brace the bridge in the plane of the macrocycle. Computational experiments produced several low energy conformations available to this bridged analog (6 families within 5 kcal/mol). All of the conformational families that were produced in this search showed the bridge in the proper and expected orientation. The minor differences between the families consisted of small spatial orientation changes in some of the functional groups about the periphery of the molecule. It is important to report, since we are concerned primarily with the orientation of the functional groups on the periphery of the molecule, that not all of these low energy conformational families showed good overlap with the epothilone X-ray conformation. However, unlike the saturated bridged analog **5**, which showed no conformational families possessing the desired conformation, one of these low energy conformations did show excellent overlap with the epothilone X-ray conformation. Although this was not the lowest energy conformation available to **5**, being that there was such a finite number of low energy conformations available to **5**, statistically there was good probability that the molecule would exist in this orientation for adequate time for binding to occur. Figure 8 below shows this low energy conformation on the left and its overlap with the epothilone X-ray conformation on the right of the figure (where the bridged analog is shown in green and the epothilone X-ray conformation is shown in gray).

Figure 8



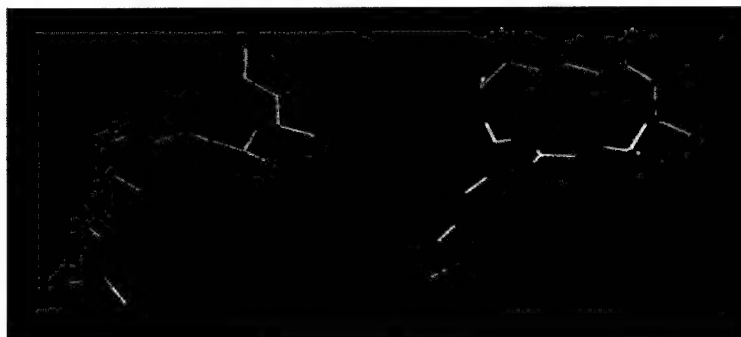
While we had now addressed the problems with our conformationally-restricted epothilone analog, we were still in search of an eastern hemisphere analog which could mimic the "hot spot" region of the epothilone molecule. The design of such an analog would allow us to determine if this hemisphere of the epothilone molecule on its own was sufficient for inducing a biological response. Our initial eastern hemisphere analog **28** had failed to provide the correct conformation of the "hot spot" region of the molecule. This failure was grounded in the fact that there were simply too many low energy conformations available to **28** for there to be any degree of certainty that any one conformation (i.e. the required conformation for binding) would be sufficiently populated. In an effort to find a way of minimizing the number of conformational families available to our eastern hemisphere analog, we designed an even more constrained eastern hemisphere analog. To this end, we began considering the possibility of preparing a ten-membered ring eastern hemisphere analog. By restricting the ring size from eleven to ten we hoped to limit the number of conformations available to our ring. Figure 10 illustrates this second generation eastern hemisphere analog.

Figure 9



Molecular modeling studies (Monte Carlo conformational searches performed in MacroModel) on the ten-membered ring eastern hemisphere analog confirmed that there was, in fact, a much more restricted number of low energy conformations available to this ring, as compared to the eleven-membered ring. Much to our delight, further examination of the lowest energy conformational families of **39** showed that the lowest energy conformation available to this molecule showed excellent overlap with the "hot spot" region of the epothilone X-ray conformation. Figure 10 shows the lowest energy conformation available to **39** on the left and the overlap of **39** (shown in blue) with the epothilone X-ray (shown in gray) on the right. It is easy to notice the exceptional conformity between these two molecules in the "hot spot" region of the molecule.

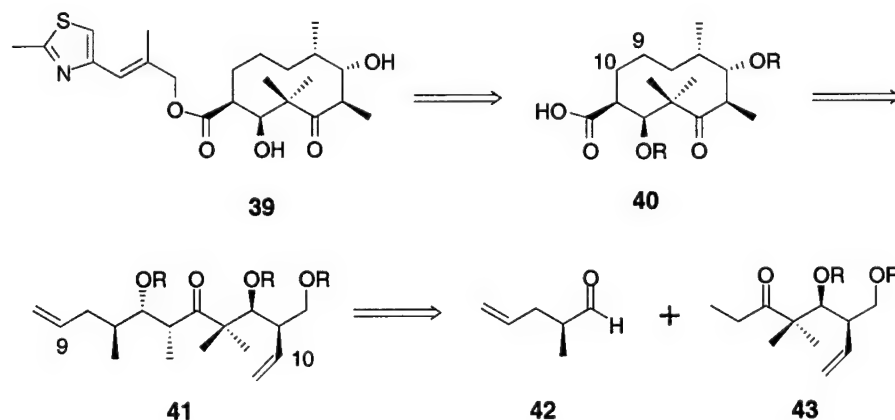
Figure 10



The project at this point became focused on the preparation of this second generation, ten-membered ring eastern hemisphere analog.

The retrosynthetic analysis of the ten-membered ring eastern hemisphere analog **39** is shown in Scheme 8 below and paralleled that for the initial eleven-membered ring eastern hemisphere analog. We saved attachment of the aromatic side chain for the end of the synthesis, thus our synthetic task was reduced to the preparation of the ten-membered ring acid **40**. We proposed that this ten-membered ring could be prepared by a ring-closing olefin metathesis reaction of the bis-terminal olefin **41**, followed by hydrogenation of the resulting mixture of alkenes (and further protecting group and oxidative manipulations). The position of the olefin in the cyclodecene before hydrogenation is indicated in the scheme by numbers matching the corresponding carbons in the bis-terminal olefin predecessor. Bis-terminal olefin **41** could be prepared by a diastereoselective aldol reaction of aldehyde **42** and ethyl ketone **43**. Aldehyde **42** and ethyl ketone **43** could both be prepared in optically active form using an acylated Evans' chiral auxiliary for asymmetric induction.

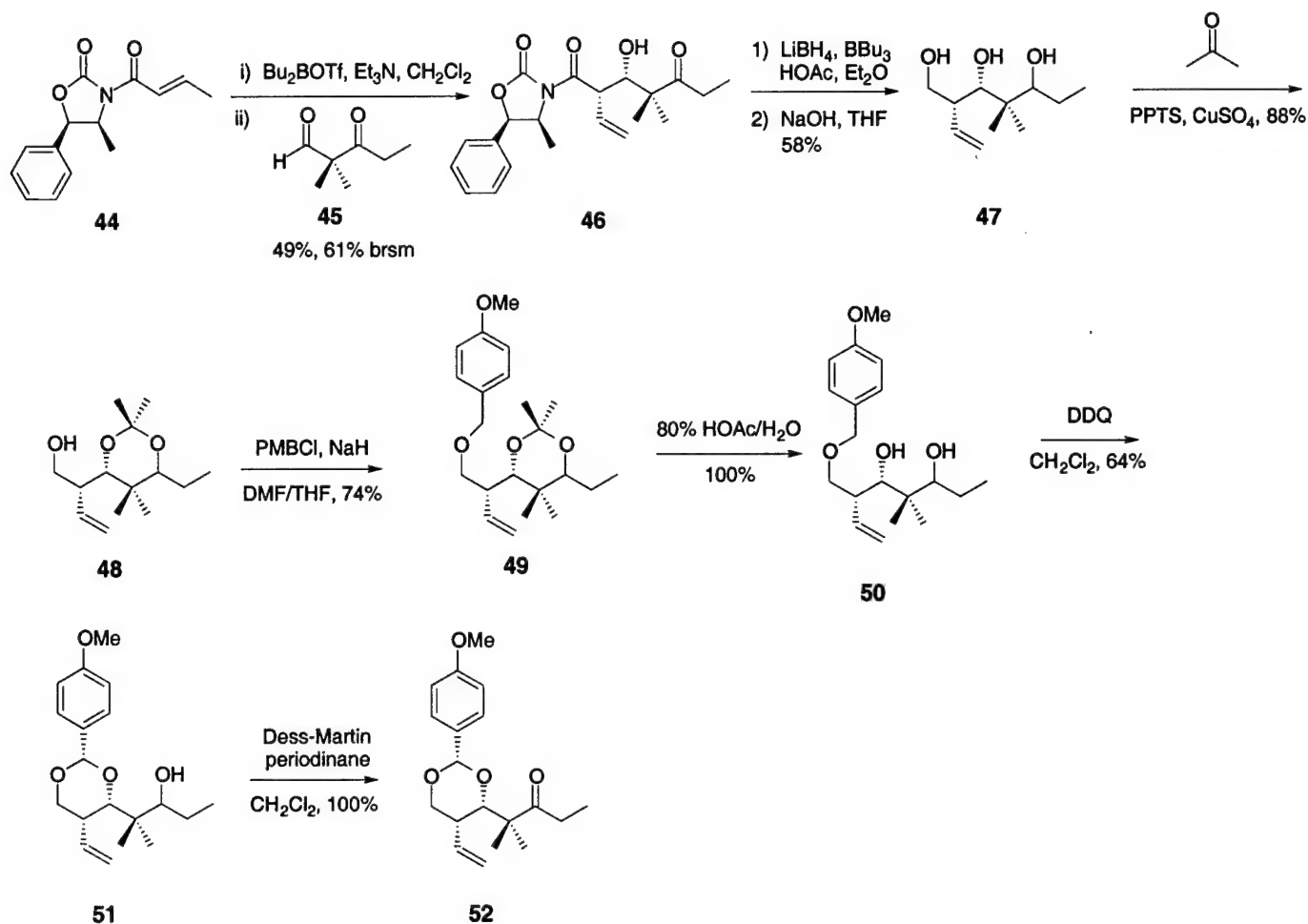
Scheme 8



Synthesis of the ethyl ketone subtarget **43** began with the preparation of triol **47**, as shown in Scheme 9 below. The crotonyl acylated auxiliary **44** underwent an aldol reaction with known keto-aldehyde **45** in the presence of Bu_2BOTf and Et_3N to give aldol adduct **46**. This aldol reaction results in deconjugation to give the product of condensation at the α position. Reductive removal of the chiral auxiliary and reduction of the ketone was accomplished using LiBH_4 to provide triol **47**. Tributylborane was used as a chelating agent in the reduction reaction in order to suppress retro-aldol fragmentation (as this highly conjugated system would be otherwise prone to such fragmentation). For this particular

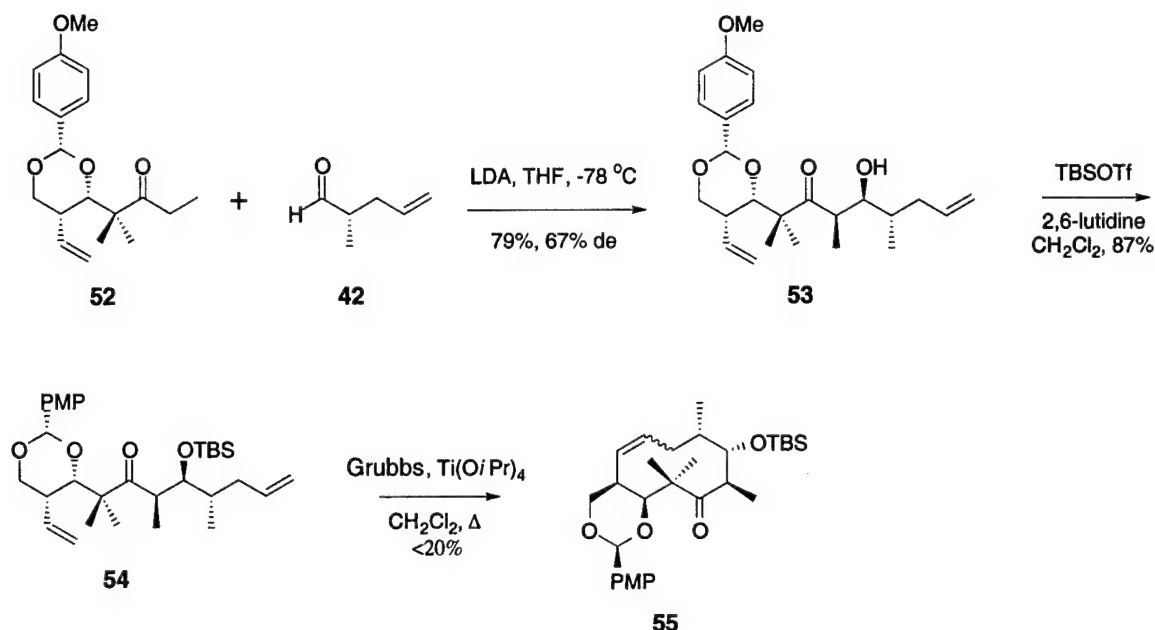
substrate, a basic hydrolysis step was needed in addition to the standard workup conditions in order to free the triol from its boron complex.

Scheme 9



As is shown in Scheme 9, triol **47** could be selectively protected at its internal secondary hydroxyls to provide the acetonide **48** by treatment with PPTS and copper sulfate in acetone for several days. Next, the primary hydroxyl could be protected as its PMB ether **49**. The acetonide was then removed under acidic conditions to provide diol **50** in quantitative yield. The PMB group could then be oxidized with DDQ to tie over to the neighboring secondary hydroxyl group, furnishing cyclic diol protection as in **51**. Finally, the remaining secondary hydroxyl was oxidized with Dess-Martin periodinane to afford ethyl ketone **52** in quantitative yield. Overall, while this route was longer than we had initially planned, it proved to be extremely efficient for the preparation of **52**.

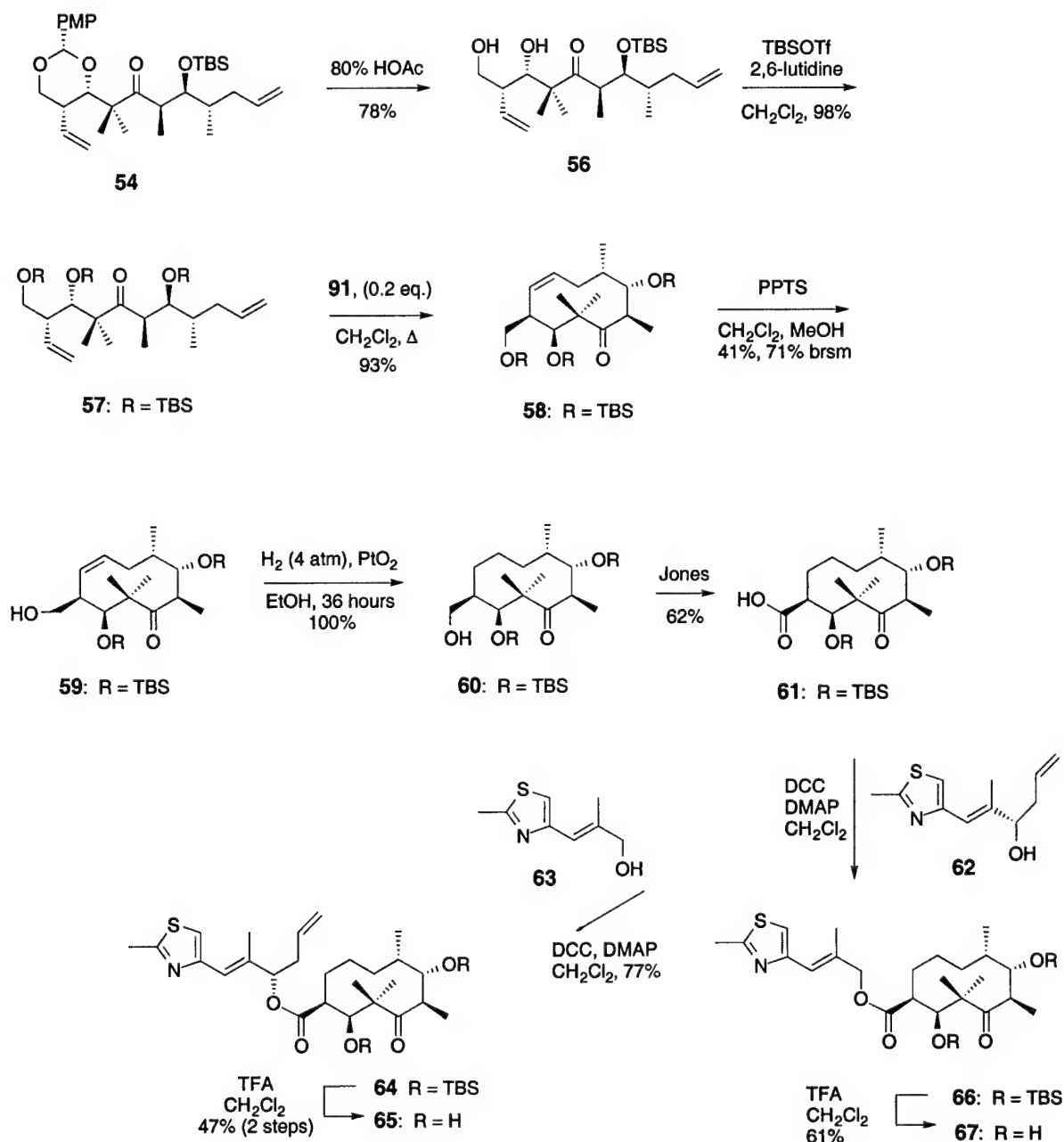
Scheme 10



With aldehyde **42** and ethyl ketone **52** in hand, the next step was their coupling as is shown in Scheme 10. The aldol reaction provided **53** as a 5:1 mixture of diastereomers (67% diastereomeric excess) with the major product formed in 79% yield. The stereochemistry of the major diastereomer was first assigned based on analogy to previous synthetic studies and was later confirmed by X-ray crystallographic analysis of a crystalline descendent produced later in the synthesis.

Having accomplished the aldol reaction, we now were preparing for macrocyclization. Hydroxyl **53** could be protected as its corresponding TBS ether to provide bis-terminal olefin **54**. With **54**, we were now poised to attempt the ring-closing olefin metathesis reaction. The initial conditions which were attempted simulated the conditions which had been successful at providing cyclization for the eleven-membered ring metathesis reaction. Thus, bis-terminal olefin **54** was treated with Grubbs' catalyst and titanium tetraisopropoxide¹⁴ in refluxing methylene chloride. Unfortunately, these conditions failed to provide the desired cyclodecene **55** in satisfactory yields. The desired product could only be detected in yields less than 20% yield. In addition to the desired product, a significant amount of dimer was produced, as well as some yet-to-be-identified byproduct.

Scheme 11

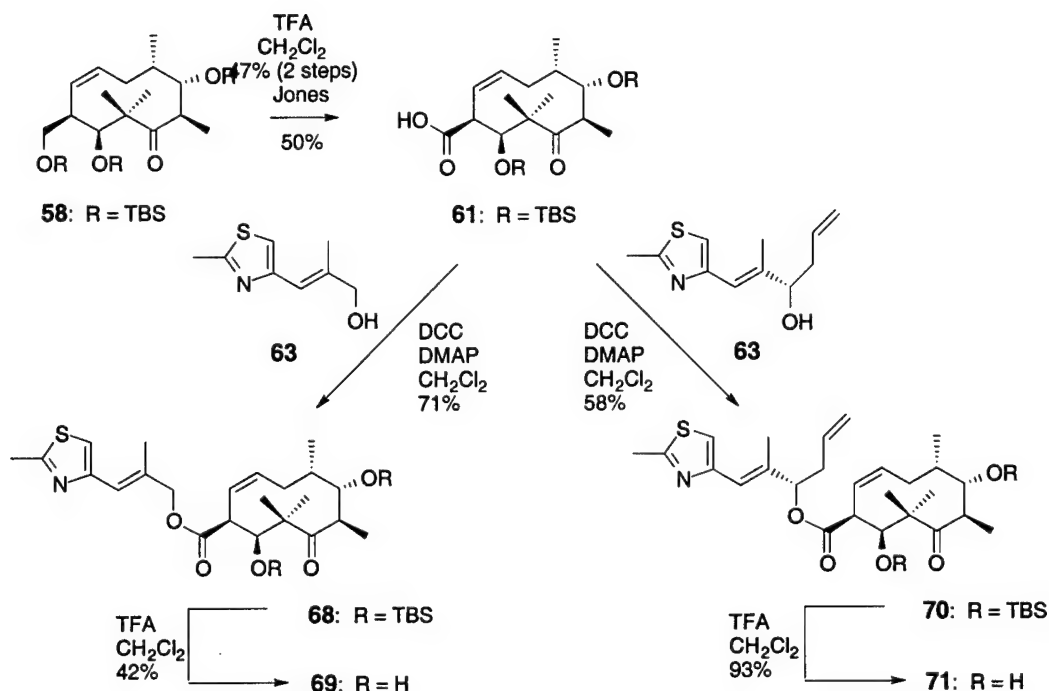


Faced with these difficulties in the metathesis reaction, we speculated that the substrate **54** was simply too constrained to undergo facile cyclization. Perhaps having the cyclic acetal in tact was introducing enough strain into the system such that cyclization was extraordinarily disfavored. In order to probe this theory, the cyclic benzylidene acetal in **54** was deprotected using aqueous acetic acid to provide the corresponding diol **56**. The two hydroxyls were then protected as their corresponding TBS ethers by treating **56** with excess TBSOTf and 2,6-lutidine to give tri-TBS ether **57**. This acyclic metathesis substrate was then treated with Grubbs' catalyst in refluxing methylene chloride. Much to our jubilation, the reaction proceeded smoothly to provide the desired cyclodecene **58** in excellent yield. This metathesis reaction was

very interesting for a couple of reasons. First, it did not require the use of a Lewis acid additive for the success of the cyclization. Although the oxygens in this molecule were positioned so as to allow both five- and six-membered intramolecular chelates between the evolving metallacarbene and heteroatoms in the molecule, they did not interfere with the reaction. Presumably, this was due to the inaccessibility of oxygen lone pairs of sterically encumbered silyl ethers for coordination.¹⁰ The second noteworthy point about this metathesis reaction was that it furnished only one olefin isomer; *the cis cyclodecene was formed exclusively in this ring-closing metathesis reaction.*

Since prolonged reaction conditions were required for our system in order to achieve consumption of starting material, we do not know if the E-isomer was initially formed in any substantial quantity in our metathesis reaction. However, computational analysis of our system did not indicate that such a thermodynamic preference for the Z-isomer over the E-isomer existed. In fact, conformational searches for both isomers using the MM2* force field in MacroModel showed less than a 1 kcal/mol difference between the two possible products.

Scheme 12



With cyclodecene **58** in hand, we were now equipped to complete the synthesis of our ten-membered ring eastern hemisphere analog. Scheme 59 shows the final steps of the synthesis of **61**. First, selective deprotection of the primary TBS ether in the presence of the two secondary TBS ethers was accomplished using PPTS in methylene chloride and methanol to give alcohol **59**. Substrate **59** was then subjected to hydrogenation conditions; treatment of **59** with four atmospheres of hydrogen and platinum oxide for 36 hours was required for the hydrogenation of this olefin. This provided cyclodecane **60** in quantitative yield. The primary alcohol was then oxidized in one step using Jones reagent to provide acid **61** in 62% yield. This acid was then coupled to the known alcohol **62** using DCC and DMAP in methylene chloride to provide ester **66** in 77% yield. This di-TBS ether was fully deprotected using TFA in methylene chloride to provide the desired ten-membered ring eastern hemisphere analog **67**. We also prepared analog **65** from acid **61** by first coupling to known alcohol **63** followed by silyl ether

deprotection. This analog was prepared for the purpose of more closely imitating the natural product. Analog **65** contained three more carbons than analog **67**, giving it the same molecular formula as desoxyepothilone A. Analog **65** also possessed the natural stereochemistry at C15. We speculated, then, that since **65** should closely mimic epothilone in terms of its hydrophobicity, solubility could be ruled out as a factor for concern in the biological evaluation of these analogs.

Since the olefin metathesis reaction had cleanly produced only one olefin isomer, we were afforded simple means of preparing two additional eastern hemisphere analogs, as in Scheme 12. When tri-TBS ether **58** was subjected directly to Jones reagent, the primary TBS ether was deprotected and the resulting primary alcohol subsequently oxidized to provide β,γ -unsaturated acid **61** in good overall yield. It should be noted that alternative means of oxidizing the primary alcohol produced mixtures of **61** with its α,β -unsaturated isomer. Acid **61** could then be coupled to alcohol **63** and alcohol **63** to provide analogs **69** and **71** after deprotection of the TBS ethers.

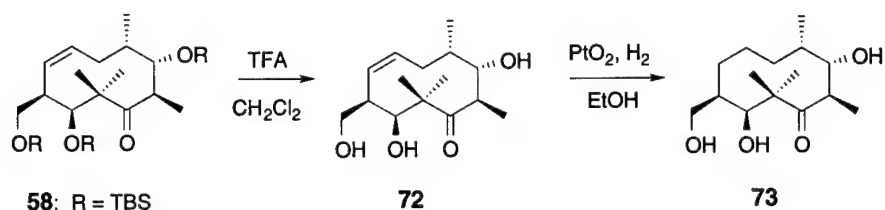
Analog **65**, **67**, **69** and **71** were sent to Dr. Susan Horwitz at the Department of Molecular Pharmacology at the Albert Einstein College of Medicine for biological testing. None of these compounds displayed activity in tubulin turbidity measurement experiments or in tubulin depolymerization experiments. What did this lack of activity mean? In order to be able to draw any conclusion from these results, we needed to first determine whether or not we had succeeded in our goal of mimicking the natural conformation of the "hot spot" region of the epothilone molecule.

The most conclusive way of determining our success, or lack thereof, in mimicking the natural conformation of the "hot spot" of epothilone was to obtain an X-ray crystal structure of our second generation eastern hemisphere analog. We did not feel that the presence of the aromatic sidechain would affect the conformation of the ten-membered ring, and molecular modeling experiments supported this opinion. Therefore, in order to sidestep material supply issues at a late point in the synthesis, we set out to obtain a crystal structure of an early intermediate in our synthetic route. It seemed obvious that we would want our crystalline compound to be as structurally similar to the final analog as possible (with the exception that it would not contain the sidechain, as discussed above), so that we could draw analogies between it and the final analogs. If the reader will recall, we had run into this difficulty when obtaining the crystal structure for our eleven-membered ring analog. The crystalline derivative that we had obtained for that analog had a TBS protecting group attached to the C7 hydroxyl. In the analysis of the resulting crystal structure, we needed to consider that this bulky protecting group could be perturbing the conformation of the eleven-membered ring in a way that the final analog may not have experienced. Consequently, we could not confidently draw conclusions about the conformation of our final analog from the crystal structure which we had obtained. We wanted to avoid making the same mistake in the analysis of this ten-membered ring analog.

Task 5. Second Generation Modeling of Epothilone Analogs

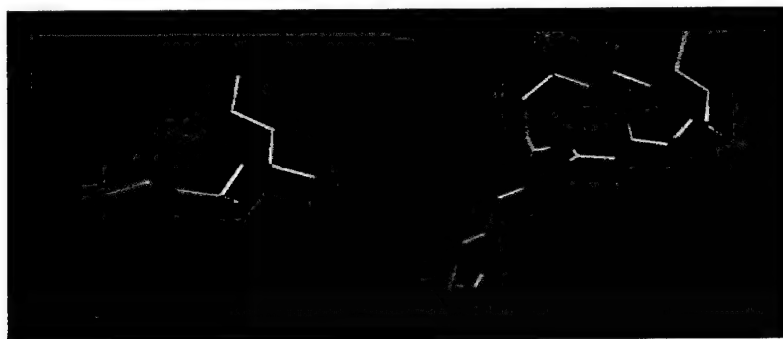
With these factors in mind, we set our sights on obtaining a crystal structure of the most simple ten-membered ring intermediate -- triol **73**. Conformational searches for triol **73** using MacroModel predicted that the lowest energy conformations available to this triol were identical to those predicted for the final analog. The low energy conformations of **73** showed excellent overlap with the epothilone X-ray conformation. Therefore, we were confident that this was the most appropriate compound for which to obtain a crystal structure. As is shown in Scheme 13 below, triol **73** was obtained by first fully deprotecting tri-TBS ether **58**, the product of the ring-closing olefin metathesis reaction. This deprotection was affected by treating the tri-silyl ether with trifluoroacetic acid in methylene chloride to give **72**. The resulting cyclodecene triol **72** was hydrogenated using platinum oxide and hydrogen (at atmospheric pressure) to produce triol **73** cleanly.

Scheme 13



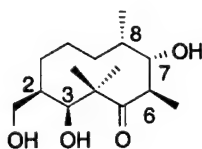
After a variety of conditions was attempted, crystals of triol **73** were finally grown by slow evaporation of ether at 0 °C, and the crystal structure of triol **73** was solved by Dr. Pat Carroll. Interestingly, Dr. Carroll found two triol molecules hydrogen bound to one water molecule. Upon examination of the three dimensional structure in MacroModel, we were able to determine that the conformation of both triol molecules in this "dimer" were identical. The X-ray conformation of triol **73** is shown in the left of Figure 28 below. Analysis of this conformation using MacroModel showed that this conformation matched the low energy conformation obtained in the Monte Carlo conformational searches. Overlap of the X-ray conformation of triol **73** with the appropriate region of the epothilone X-ray conformation is shown on the right of Figure 11. Triol **73** is shown in red and the epothilone X-ray conformation is shown in gray. As the reader can see from this picture, triol **73** showed excellent overlap with "hot spot" region of the epothilone X-ray conformation.

Figure 11



The next task ahead of us was to examine the relationship between the X-ray conformation of **73** and its solution conformation. We felt that the best way to probe the solution conformation of **73** would be to study its proton NMR spectrum. Since the Karplus relationship correlates coupling constants to bond angles, examination of the crystal structure should tell us what to expect for coupling constants. From the spatial coordinates of the protons in the crystal structure, MacroModel could predict what the coupling constants in that conformation would be. We could then compare those predicted coupling constants to the observed solution state coupling constants. To this end, the proton NMR spectrum for **73** was obtained in 75% DMSO (fully deuterated) and 25% D₂O. Table 2 shows the coupling constants predicted by MacroModel for **73** along with the observed coupling constants obtained for **73**. What the reader will notice is that there was excellent agreement between the predicted values and the observed values for the 2, 3 coupling constants and the 7, 8 coupling constants. However, there was a 1.9 Hz discrepancy for the 6, 7 coupling constants (corresponding to approximately a 30° dihedral angle difference). We felt that this difference could be due, at least in part, to environmental influences the triol may have been experiencing in solution as compared to the "gas phase" predictions from MacroModel. We needed to extend our analysis further to determine if our final analog was adopting the proper conformation.

Table 2

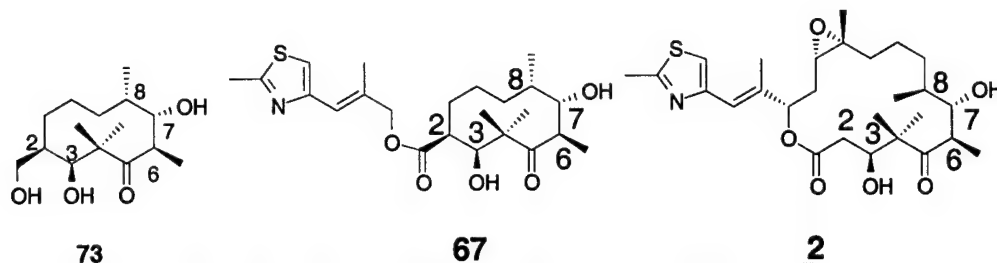


73

Coupling Protons	<i>J</i> (Hz) Predicted from X-ray by MacroModel	<i>J</i> (Hz) Observed in Solution 75% DMSO / 25% D ₂ O
2, 3	1.5	< 1
6, 7	10.6	8.7
7, 8	< 1	2.0

To extend our examination we would compare the solution conformations of triol **73**, our final analog **67** and epothilone (**2**). We had hypothesized that the presence of the aromatic sidechain would not perturb the conformation of the cyclodecane from the conformation seen in **73**, and molecular modeling supported that hypothesis. In order to test this hypothesis, we chose, again, to perform a comparison of the solution conformations of these compounds by studying their proton NMR spectra. Table 2 illustrates this comparison by showing the coupling constants obtained for the "hot spot" region of **73**, those for the corresponding region of our final analog **67** and those for the epothilone molecule. The spectra for all of these molecules were obtained in the same manner, using 75% DMSO/25% D₂O at 500 MHz. There was excellent correspondence between the values for **73** and **67**. From these results we concluded that the solution conformation of our final analog **67** correlated well with the solution conformation of **73**, as we had originally hypothesized. In addition, the coupling constants for both **73** and **67** showed excellent correlation with those for the natural product, **2**, in the C6 through C8 region of the molecule. There was at least a 2 Hz discrepancy between the 2, 3 coupling constants, however. Molecular modeling examination of the desired dihedral angle between the 2 and 3 protons of **73** and **67** suggested that the corresponding coupling constant should be 1.5 Hz, in agreement with the observed values. Furthermore, examination of the dihedral angle between the 2b and 3 protons of the X-ray crystal structure of epothilone suggested that that coupling constant should also be 1.5 Hz. From this data we felt that we could conclude that the conformations of our analogs mimicked that of the X-ray crystal structure of epothilone. The discrepancy observed in solution could be due to the difference in substitution of the C2 position of our analogs as compared to the natural product.

Table 3



Coupling Protons	<i>J</i> (Hz)	<i>J</i> (Hz)	<i>J</i> (Hz)
2a, 3	----	----	11.0
2b, 3	< 1	< 1	3.0
6, 7	8.7	8.2	9.0
7, 8	2.0	< 1	< 1

Without having actually performed similar analyses on analog **65**, we felt that we could extend the conclusions reached above for analog **67** to analog **65**. Undeniably, the presence of the additional allyl unit extending from the sidechain should be inconsequential to the conformation of the cyclodecane ring itself. As such, we believed that the conformation of **65** in the "hot spot" region of the molecule was identical to that in **67**. From the above analyses, we concluded that we had, in fact, succeeded in accomplishing what we had set out to do in this project -- *we had successfully designed and synthesized novel eastern hemisphere analogs of epothilone which closely mimicked the conformation of the natural product in the crucial "hot spot" region of the molecule.*

KEY RESEARCH ACCOMPLISHMENTS:

- * New analogs of the potent antitumor substance epothilone have been prepared
- * We have established that Macromodel is a superior modelling package for the evaluation of the conformational flexibility of these novel structures; and
- * Biological evaluation of these new compounds (cytotoxicity and tubulin polymerization) indicates that they are NOT biologically active.

REPORTABLE OUTCOMES:

A publication has appeared in print describing the first generation left- and right- hand analog synthesis of epothilone;

A full paper is being prepared based on the results outlined in this final report;

Joanne Holland has obtained a Ph.D. degree and Jiri Kaspárec has obtained an M.S. degree during the course of the research;

Joanne Holland is now a research scientist at Sepracor and Jiri Kaspárec is a Research Associate at Dupont Pharmaceuticals.

CONCLUSIONS:

What remains for this author to provide is an explanation for the lack of biological activity for our second generation eastern hemisphere analogs **67** and **65**. The preceding section served to explain that our analogs do mimic the X-ray conformation of epothilone in the "hot spot" region of the molecule. Consequently, they are in the truest sense of the words, eastern hemisphere analogs of epothilone. They contain all of the functionality of the eastern hemisphere of the natural product, and they possess the conformation of the eastern hemisphere of the natural product. By having obtained the biological evaluation of analog **65** in addition to analog **67**, we can rule out the possibility of solubility problems interfering with the biological activity of these analogs, as analog **65** possesses the same molecular formula as desoxyepothilone A (which shows a similar biological profile as epothilone A).¹⁷

Although the eastern hemisphere and the aromatic sidechain have been labeled as perhaps the most crucial regions of the molecule, the remainder of the macrocycle clearly serves an important role. We believe that our results allow us to conclude that the function of the remainder of the epothilone molecule must be important for something other than simply placing the eastern hemisphere of the molecule in the appropriate conformation or providing the most advantageous hydrophobicity profile. We believe, then, that we can conclude from our work that if the epothilone X-ray conformation is the active conformation of this natural product, the eastern hemisphere of the molecule is not sufficient on its own for eliciting the biological response attributed to epothilone.

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¹¹For the grouping of families for bridged analog, the classifications were based on the overlap of the macrocycle; overlap of the aromatic sidechain was not considered, as there were too many degrees of freedom to take into account for practical reasons.

¹²This time we only considered the "hot spot" region of the molecule when classifying the produced conformations into families, as the conformation of the tether connecting C2 to C10 of this analog was not important to us.

¹³This anomaly extended to conformational searches for the X-ray derivative **37** which predicted several low-lying energy conformations for that eleven-membered ring as well, none of which matched its X-ray structure.

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APPENDICES:

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BIRTH DATE: April 14, 1956

EDUCATION:

Post-doctoral: Columbia University. January 1982-August 1983.
Research Director: Professor Ronald Breslow.

Graduate: Columbia University. September 1977-December 1981.
M.A. 1978, M.Phil., Ph.D. 1981.
Thesis Advisor: Professor Gilbert Stork.

Undergraduate: Harvard College. September 1973-June 1977.
A. B. cum laude in Chemistry, 1977.

PROFESSIONAL EXPERIENCE:

Merriam Professor of Chemistry,
University of Pennsylvania, January 2001-

Professor, University of Pennsylvania
Department of Chemistry, July 1996-

Founding Member, University of Pennsylvania
Center for Cancer Pharmacology, May 1998-present

Associate Professor, University of Pennsylvania,
Department of Chemistry, July 1990-June 1996

Member, University of Pennsylvania Cancer Center,
July 1993-present

Assistant Professor, University of Chicago,
Department of Chemistry, September 1983-June 1990

AWARDS & HONORS: American Chemical Society Cope Scholar Award, 2000
Parke-Davis Lecturer, Michigan State University, 2000
Chairman, Philadelphia Organic Chemists' Club, 1995
H. Martin Friedmann Lecturer, Rutgers University, 1993
American Cyanamid Young Faculty Award, 1989-1992
NIH-NCI Research Career Development Award, 1988-1993
Alfred P. Sloan Research Fellow, 1987-1989
Merck Foundation Award for Faculty Development, 1985
American Cancer Society Postdoctoral Fellow, 1982-1983

PROFESSIONAL ACTIVITIES

Consultant, Wyeth-Ayerst Pharmaceuticals (1998-)
Associate Editor, *Organic Letters* (1999-)

INVITED LECTURES SINCE 1990:

Merck, Sharp & Dohme (West Point, PA)
Smith, Kline and Beckmann
Invited Lecturer, Symposium on Organic Synthesis, Great Lakes Regional ACS Meeting, Dekalb, Illinois
Invited Lecturer, Molecular Recognition Meeting, Office of Naval Research, Charleston, S.C
Invited Lecturer, Symposium on Heterocyclic Chemistry, National ACS Meeting, Washington, D.C
Squibb Institute for Medical Research (Princeton, NJ)
University of Rochester
Squibb Institute for Medical Research (New Brunswick, NJ)
Boehringer-Ingelheim Pharmaceuticals
Brandeis University
University of Delaware
ICI Pharmaceuticals
New York Academy of Sciences
North Jersey ACS Meeting
Invited Lecture, 1992 Meeting of the American Society for Photobiology
Organizer and Lecturer, Symposium on Studies Toward the Total Synthesis of Taxol, National ACS Meeting, San Francisco, CA. (April 8, 1992)
Dupont Agricultural Products
Burroughs Wellcome
University of Virginia
Sandoz Institute
Sterling Winthrop
Bryn Mawr College
Invited Lecturer, Symposium on Organic Chemistry, Great Lakes Regional ACS Meeting, Ann Arbor, Michigan
Invited Lecturer, Symposium on Organic Synthesis, Middle Atlantic Regional ACS Meeting, Baltimore, Maryland
Technion-Israel Institute of Technology
Pfizer Central Research
Sandoz Institute
Hebrew University of Jerusalem
R. W. Johnson
University of Montreal
Plenary Lecturer, Wyeth-Ayerst Fourth Annual Chemical Sciences Symposium
Merck (West Point, PA)
American Cyanamid

DAMD17-98-1-8547

Jeffrey D. Winkler, PI

Design and Synthesis of New Breast Cancer Chemotherapeutic Agents

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Rhone-Poulenc Agricultural

Plenary Lecture, Interamerican Photochemical Society

University of Maryland

R. W. Johnson Pharmaceutical Research

Wyeth-Ayerst

Sepracor

Boehringer-Ingelheim

Florida State University

Northwestern University

UCLA

University of Minnesota

Parke-Davis

Pfizer

Penn State University

Smith Kline Beecham

Temple University

Amgen

University of Chicago

Dupont Pharmaceuticals

Invited Speaker, Symposium on Solid Support Chemistry, Middle Atlantic Regional ACS Meeting, May 1999

Plenary Lecturer, Symposium on Heterocycles, Canadian Institute of Chemistry, June 1999

Invited Speaker, Gordon Conference on Heterocycles, July 2000

University of Western Ontario

Boehringer-Ingelheim, Montreal

Villanova University

Johnston Mathey

Lederle Laboratories

Genetics Institute

University of Pittsburgh

New York Academy of Sciences

Merck-Frosst Lecturer, University of Sherbrooke

Parke Davis Lecturer, Michigan State University

Bristol-Myers Squibb Lecturer, MIT

Albany Molecular Sciences

University of California, Irvine

Merck (West Point, PA)

University of Ottawa

Aventis Pharmaceuticals

PUBLICATIONS :

1. L. Blaszcak, J. Winkler, S. O'Kuhn, "A New Synthesis of Olefins from Ketones via Coupling of Lithium Dialkylcuprates with Enol Phosphate Diesters," *Tetrahedron Lett.* **1976**, 4405-4408.
2. G. Stork, C. Shiner, J. Winkler, "Stereochemical Control of the Internal Michael Reaction. A New Construction of trans-Hydrindane Systems," *J. Am. Chem. Soc.* **1982**, *104*, 310-312.
3. G. Stork, J. Winkler, C. Shiner, "Stereochemical Control of Intramolecular Conjugate Addition. A Short, Highly Stereoselective Synthesis of Adrenosterone," *J. Am. Chem. Soc.* **1982**, *104*, 3767-3768.

4. G. Stork, J. Winkler, N. Saccomano, "Stereochemical Control in the Construction of Vicinally Substituted Cyclopentanes and Cyclohexanes. Intramolecular Conjugate Addition of β -Ketoester Anions," *Tetrahedron Lett.* **1983**, 465-468.
5. J. Winkler, E. Coutouli-Argyropoulou, R. Leppkes, R. Breslow, "An Artificial Transaminase Carrying A Synthetic Macrocyclic Binding Group," *J. Am. Chem. Soc.* **1983**, *105*, 7198-7199.
6. W. Weiner, J. Winkler, S. Zimmerman, R. Breslow, "Mimics of Tryptophan Synthetase and of Biochemical Dehydroalanine Formation," *J. Am. Chem. Soc.* **1985**, *107*, 4093-4094.
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8. J. Winkler, V. Sridar, "Stereochemical Control of Transannular Radical Cyclizations. A New Approach to the Synthesis of Linearly Fused Cyclopentanoids," *J. Am. Chem. Soc.* **1986**, *108*, 1708-1709.
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10. J. Winkler, P. Hershberger, J. Springer, "A Stereoselective Synthesis of the Azaspiroundecane Ring System of (-)-Histriocotoxin from (+)-Glutamic Acid," *Tetrahedron Lett.* **1986**, 5177-5180.
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13. J. Winkler, K. Deshayes, "Photodynamic Macrocycles," *J. Am. Chem. Soc.* **1987**, *109*, 2190-2191.
14. J. Winkler, K. Henegar, P. Williard, "Inside-Outside Stereoisomerism II. Synthesis of the Carbocyclic Ring System of the Ingenane Diterpenes *via* the Intramolecular Dioxolenone Photocycloaddition," *J. Am. Chem. Soc.* **1987**, *109*, 2850-2851.
15. K. Henegar, J. Winkler, "A New Method for the Synthesis of Dioxolenones *via* the Carboxylation of Ketone Enolates with Anisyl Cyanoformate," *Tetrahedron Lett.* **1987**, 1051-1054.
16. J. Winkler, C. Muller, R. Scott, "A New Method for the Formation of Nitrogen-Containing Ring Systems *via* the Intramolecular Photocycloaddition of Vinylogous Amides. A Synthesis of Mesembrine," *J. Am. Chem. Soc.* **1988**, *110*, 4831-4832.
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20. J. Winkler, P. Hershberger, "A Stereoselective Synthesis of (-)-Perhydrohistriocotoxin," *J. Am. Chem. Soc.* **1989**, *111*, 4852-4856.

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71. Y. Kwak, J. Winkler, "Synthesis of 6-Aza-Bicyclo[3.2.1]Octan-3-Ones via Vinylogous Imide Photochemistry: An Approach to the Synthesis of the Hetisine Alkaloids," *J. Am. Chem. Soc.* **2001**, in press.

2. EXPERIMENTAL PROCEDURES

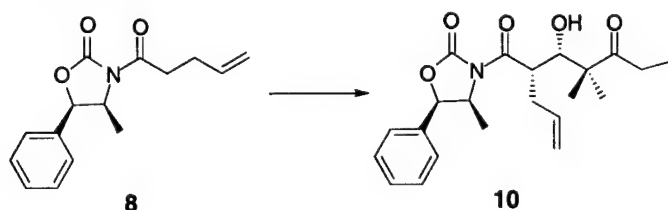
All reactions were carried out under an argon atmosphere using dry glassware. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Benzene, toluene, acetonitrile, triethylamine, hexamethylphosphoric triamide (HMPA), diisopropylamine and dichloromethane (DCM) were distilled from calcium hydride. Commercial reagents were used as received.

Thin layer chromatography was performed on 0.25 mm silica gel plates from Merck. The plates were visualized with UV-light followed by staining with phosphomolybdic acid, ceric sulfate, anisaldehyde or potassium permanganate. Flash column chromatography was performed using 230-400 mesh (particle size 0.04-0.063 mm) silica gel supplied by Mallinckrodt or E. Merck.

Small scale thermal Diels-Alder reactions were carried out using a J. Young resealable NMR tube with a teflon valve.

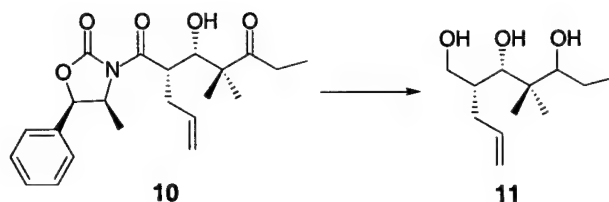
Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR spectrophotometer and were recorded neat on a KBr plate. Unless otherwise noted, NMR spectra were obtained on a Bruker AMX-500 spectrometer using deuterated chloroform as solvent. ^1H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125.7 MHz respectively and referenced as δ 7.24 for proton and δ 77.0 for carbon. High resolution mass spectra were obtained by Mr. John Dykins, Dr. Rakesh Kohli and Ms. Magda Cuevas at the University of Pennsylvania Mass Spectrometry Service Center on either a VG micromass 70/70H high resolution double-focusing electron impact/chemical ionization spectrometer or a VG ZAB-E spectrometer. Single-crystal X-ray diffraction structure determination was performed by Dr. Pat Carroll and Dr. Sang Wook Kang at the University of Pennsylvania. Optical rotations were measured at 20 °C on a Perkin-Elmer 341 polarimeter.

Preparation of **8**:

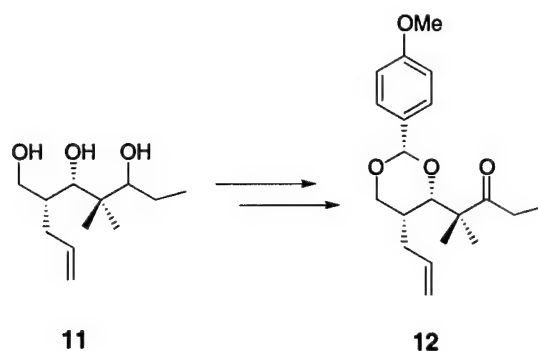


To a solution of **8** (40.723 g, 0.157 mol) in methylene chloride (319 mL) at 0 °C was added dibutylborontriflate (146 mL, 1.0 M in methylene chloride, 0.146 mol) followed by freshly distilled triethylamine (26.611 mL, 0.191 mol) extremely slowly so as to prevent the internal temperature from

rising above 3 °C. The resulting pale yellow solution was cooled to -78 °C before adding aldehyde **9** (14.375 g, 0.112 mol) in methylene chloride (6 mL) slowly. The resulting solution was allowed to continue stirring at this temperature for 10 minutes before warming to 0 °C and stirring for three hours. The reaction was then quenched by the addition of aqueous pH 7 phosphate buffer followed by methanol, all at a rate so as to keep the internal temperature below 10 °C. Next, a 2:1 solution of methanol:30% hydrogen peroxide was added slowly, again maintaining the reaction temperature below 10 °C, and the resulting mixture allowed to warm to room temperature and stir for one hour. The volatile material was then removed *in vacuo* and the resulting mixture further diluted with diethyl ether, the organic layer separated and the aqueous later further extracted with diethyl ether. The combined organics were washed with a saturated aqueous solution of sodium bicarbonate followed by brine, dried (MgSO₄), concentrated *in vacuo*, and the residue purified by flash column chromatography using a gradient of 5% to 50% ethyl acetate-petroleum ether to give the desired aldol adduct **10** (21.126 g, 49%; 65% based on recovered starting acylated oxazolidinone): ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.41 (m, 3 H), 7.28-7.29 (m, 2 H), 5.77-5.85 (m, 1 H), 5.68 (d, 1 H, *J* = 7.3 Hz), 4.95-5.02 (m, 2 H), 4.71 (quin, 1 H, *J* = 6.9 Hz), 4.24 (q, 1 H, *J* = 6.5 Hz), 4.13 (t, 1 H, *J* = 6.5 Hz), 3.00 (d, 1 H, *J* = 6.6 Hz), 2.56 (q, 2 H, *J* = 7.3 Hz), 2.48 (t, 2 H, *J* = 7.2 Hz), 1.23 (s, 3 H), 1.17 (s, 3 H), 1.02 (t, 3 H, *J* = 7.1 Hz), 0.82 (d, 3 H, *J* = 6.6 Hz); ¹³C NMR (125.7 MHz, CDCl₃) δ 217.4, 175.0, 152.8, 134.9, 133.3, 128.8, 128.7, 125.7, 117.4, 78.8, 76.4, 55.1, 51.8, 44.1, 34.2, 31.5, 21.9, 21.4, 14.6, 7.8; IR (neat) 3498, 1780, 1697, 1343, 1195 cm⁻¹; HRMS calculated for C₂₂H₂₉NO₅ [M + NH₄]⁺ 405.2389, found 405.2394; [α]_D²⁰ -12.7 ° (c 1.00, CHCl₃).

Preparation of **11**:

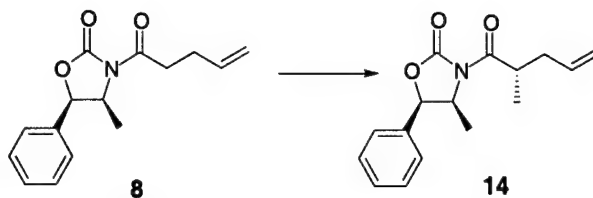
To a solution of aldol adduct **10** (870 mg, 2.25 mmol) in diethyl ether (44 mL) was added water (89 μ L, 4.95 mmol) and the solution cooled to 0 °C. Lithium borohydride (2.5 mL, 2.0 M in THF, 4.95 mmol) was then added dropwise and the resulting milky mixture stirred for one hour at 0 °C followed by three hours at room temperature. The reaction was then quenched by the addition of 1M NaOH and the mixture stirred until both layers became clear. The organic layer was then separated and the aqueous layer further extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 40% to 60% ethyl acetate-petroleum ether to give the desired triol **11** (309 mg, 63%) as a 2.3:1 mixture of diastereomers: ^1H NMR (500 MHz, CDCl_3) δ 5.77-5.85 (m, 1 H), 4.98-5.07 (m, 2 H), 3.85-3.86 (m, 1 H), 3.60-3.76 (m, 4 H), 3.33-3.45 (m, 1 H), 3.11 (br s, 0.7 H), 2.76 (br s, 0.3 H), 2.37-2.40 (m, 0.3 H), 2.29-2.34 (m, 0.7 H), 2.11-2.21 (m, 1 H), 1.79-1.82 (m, 0.7 H), 1.68-1.72 (m, 0.3 H), 1.52-1.57 (m, 1 H), 1.35-1.42 (m, 0.3 H), 1.26-1.34 (m, 0.7 H), 0.98 (t, 0.9 H, $J = 7.3$ Hz), 0.96 (t, 2.1 H, $J = 7.3$ Hz), 0.95 (s, 0.9 H), 0.94 (s, 2.1 H), 0.88 (s, 0.9 H), 0.77 (s, 2.1 H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 137.7, 137.5, 116.0, 115.9, 82.5, 81.7, 81.1, 80.1, 66.0, 65.8, 41.7, 41.0, 40.4, 40.3, 29.8, 29.7, 24.4, 24.1, 22.0, 21.6, 21.1, 15.6, 11.4, 11.2; IR (neat) 3344, 1640, 1470 cm^{-1} ; HRMS calculated for $\text{C}_{12}\text{H}_{24}\text{O}_3$ $[\text{M} + \text{H}]^+$ 217.1803, found 217.1809.

Preparation of **12**:

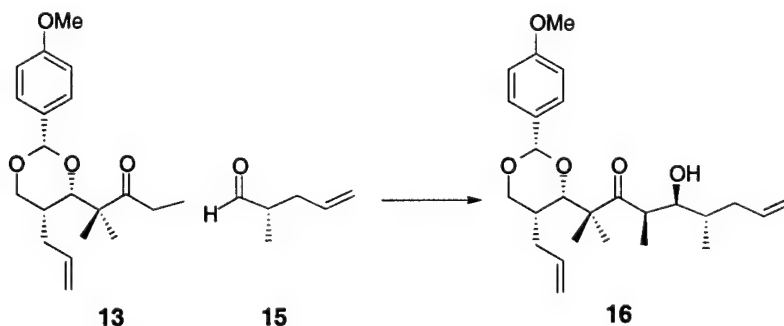
To a solution of triol **11** (1.24 g, 5.04 mmol) in DCM (20 mL) at -78°C was added anisaldehyde dimethylacetal (946 μL , 5.54 mmol) followed by camphorsulfonic acid (117 mg, 0.504 mmol) and the reaction allowed to continue stirring at this temperature for one hour before quenching by the addition of a saturated aqueous solution of NaHCO_3 . The mixture was allowed to warm to room temperature before further diluting with water and extracting with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated *in vacuo*, and the residue purified by flash column chromatography using 10% ethyl acetate-1% triethylamine-petroleum ether to give the benzylidene acetal (1.240 g, 74%, 91% based on recovered starting material) as a mixture of regioisomers. Separation of the regioisomers was not accomplished, but instead the mixture was carried to the next step.

To a solution of the regioisomeric mixture of alcohols (31 mg, 0.092 mmol) in methylene chloride (1 mL) at 0°C was added Dess-Martin periodinane reagent (118 mg, 0.28 mmol). The reaction was then warmed to room temperature and allowed to continue stirring for 2 hours. The reaction mixture was poured into 2M NaOH and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using 10% ethyl acetate-petroleum ether to give the desired ketone **12** (15 mg, 55% for two steps).

On larger scale oxidation reactions, the resulting mixture of aldehyde and ketone was inseparable via column chromatography. In such cases, the aldehyde was removed from the mixture by selectively reducing it in the presence of the ketone (and then separating the corresponding primary alcohol from the desired ethyl ketone via column chromatography). The following is a typical procedure for this manipulation: To a solution of NaBH_4 (14 mg, 0.0376 mmol) in ethanol (2.25 mL) and DCM (3.25 mL) at -78°C was added a solution of the mixture of aldehyde and ketone (250 mg, 0.753 mmol) in DCM (2 mL). The reaction was allowed to continue at this temperature for one hour at which time some additional NaBH_4 (approx. 0.2 equiv) was added and the reaction allowed to continue for an additional two hours. The reaction was then quenched by the addition of aqueous pH 7 phosphate buffer, allowed to warm to room temperature and extracted between aqueous pH 7 phosphate buffer and diethyl ether. The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and the residue purified by flash column chromatography using a gradient of 5% to 20% ethyl acetate-1% triethylamine-petroleum ether to give the desired benzylidene acetal ketone **13** (104 mg, 42%) (successfully separated from the reduced alcohol regioisomer: ^1H NMR (500 MHz, CDCl_3) δ 7.40 (d, 2 H, $J = 8.6$ Hz), 6.89 (d, 2 H, $J = 8.7$ Hz), 5.67-5.77 (m, 1 H), 5.46 (s, 1 H), 5.03-5.09 (m, 2 H), 4.21 (dd, 1 H, $J = 1.0, 11.4$ Hz), 4.00 (d, 1 H, $J = 2.1$ Hz), 3.81-3.84 (m, 1 H), 3.80 (s, 3 H), 2.64 (dq, 1 H, $J = 7.2, 75.4$ Hz), 2.60 (dq, 1 H, $J = 7.2, 75.4$ Hz), 2.42-2.49 (m, 1 H), 2.15-2.18 (m, 1 H), 1.61-1.64 (m, 1 H), 1.23 (s, 3 H), 1.21 (s, 3 H), 1.00 (t, 3 H, $J = 7.1$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.7, 160.0, 136.4, 131.3, 127.3, 117.1, 113.6, 102.6, 85.5, 70.2, 55.3, 50.8, 35.6, 32.6, 29.2, 23.0, 21.8, 8.2; IR (neat) 1699, 1615, 1517, 1248 cm^{-1} ; HRMS calculated for $\text{C}_{20}\text{H}_{28}\text{O}_4$ $[\text{M} + \text{H}]^+$ 333.2065, found 333.2068; $[\alpha]_{\text{D}}^{20} -37.4^{\circ}$ (c 0.7, CHCl_3).

Preparation of **14**:

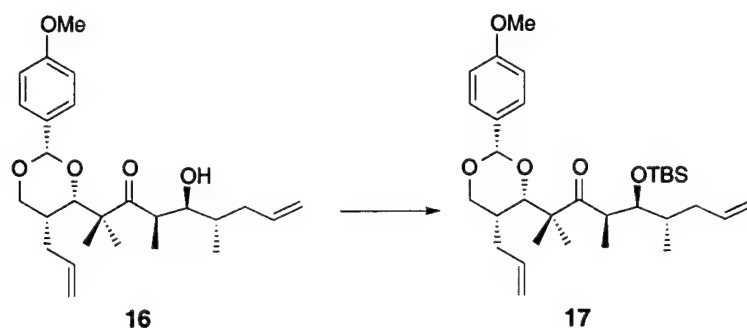
To a solution of diisopropylamine (2.976 mL, 21.2 mmol) in THF (19.75 mL) at 0 °C was added *n*-BuLi (9.114 mL, 2.33 M, 21.2 mmol) dropwise. The solution was allowed to stir at this temperature for ten minutes before cooling to -78 °C. To the LDA solution was then added a solution of **8** (5.0 g, 19.3 mmol) in THF (19.8 mL) dropwise. The resulting yellow reaction solution was allowed to continue stirring at -78 °C for 45 minutes before freshly distilled iodomethane (6.005 mL, 96.5 mmol) was added dropwise. The reaction was allowed to continue stirring at this temperature for one and one half hours before warming to -25 °C and stirring overnight. The reaction was then quenched by the addition of a saturated aqueous solution of ammonium chloride, warmed to room temperature, and extracted between aqueous ammonium chloride and diethyl ether. The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate followed by brine, dried (MgSO₄), concentrated *in vacuo*, and the residue purified by flash column chromatography using a gradient of 5% to 10% ethyl acetate-petroleum ether to give the desired **14** (2.85 g, 54%): ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.41 (m, 3 H), 7.27-7.29 (m, 2 H), 5.74-5.82 (m, 1 H), 5.62 (d, 1 H, *J* = 7.2 Hz), 5.02-5.09 (m, 2 H), 4.73 (quin, 1 H, *J* = 6.7 Hz), 3.82 (hex, 1 H, *J* = 6.9 Hz), 2.43-2.49 (m, 1 H), 2.16-2.21 (m, 1 H), 1.18 (d, 3 H, *J* = 6.9 Hz), 0.86 (d, 3 H, *J* = 6.6 Hz); ¹³C NMR (125.7 MHz, CDCl₃) δ 176.2, 152.7, 135.5, 133.3, 128.7, 128.7, 125.6, 117.0, 78.8, 54.9, 37.7, 37.5, 16.8, 14.4; IR (neat) 1781, 1699, 1345, 1197 cm⁻¹; [α]_D²⁰ -11.0 ° (c 1.00, CHCl₃).

Preparation of **16**:

To a solution of diisopropylamine (1.162 mL, 8.29 mmol) in THF (15.8 mL) at 0 °C was added *n*-BuLi (3.565 mL, 2.30 M, 8.22 mmol) dropwise. The solution was allowed to stir at this temperature for ten minutes before cooling to -78 °C and maintaining at that temperature for several hours before use. To the LDA solution was then added a solution of benzylidene acetal ketone **13** (2.479 g, 7.47 mmol) in THF (7.3 mL) dropwise and the resulting solution allowed to stir at this temperature for one hour. To the enolate solution was then added a solution of **15** (805 mg, 8.21 mmol) in THF (7 mL) dropwise. The reaction was allowed to continue at -78 °C for 20 minutes, was then quenched by the addition of a saturated aqueous solution of NH₄Cl and was allowed to warm to room temperature. The mixture was diluted further with water and the aqueous layer extracted with ethyl acetate. The combined organic extracts were dried (Na₂SO₄), concentrated *in vacuo*, and the residue purified by flash column chromatography using

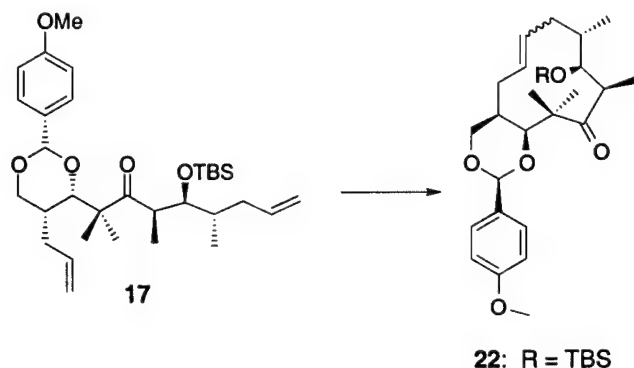
10% ethyl acetate-petroleum ether to give the desired aldol adduct **16** (1.986 g major diastereomer, 62%): ^1H NMR (500 MHz, CDCl_3) δ 7.37 (d, 2H, $J = 8.6$ Hz), 6.86 (d, 2H, $J = 8.6$ Hz), 5.65-5.79 (m, 2H), 5.44 (s, 1H), 5.08 (dd, 2H, $J = 13.6, 21.2$ Hz), 4.94-4.98 (m, 2H), 4.21-4.23 (m, 1H), 4.04 (d, 1H, $J = 2.1$ Hz), 3.82-3.84 (m, 1H), 3.78 (s, 3H), 3.46 (s, 1H), 3.36 (q, 1H, $J = 7.0$ Hz), 3.23 (d, 1H, $J = 9.4$ Hz), 2.42-2.56 (m, 2H), 2.22-2.26 (m, 1H), 1.71-1.77 (m, 1H), 1.63-1.66 (m, 1H), 1.49-1.57 (m, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.00 (d, 3H, $J = 6.9$ Hz), 0.58 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 222.9, 160.0, 137.0, 136.2, 131.0, 127.3, 117.2, 116.1, 113.5, 102.6, 85.4, 74.5, 70.2, 55.2, 51.8, 41.5, 37.3, 35.7, 35.2, 29.7, 22.7, 20.5, 14.6, 9.9; IR (neat) 3497, 1680, 1639, 1616, 1517, 1249 cm^{-1} ; HRMS calculated for $\text{C}_{26}\text{H}_{38}\text{O}_5$ $[\text{M} + \text{H}]^+$ 431.2797, found 431.2797

Preparation of **17**:



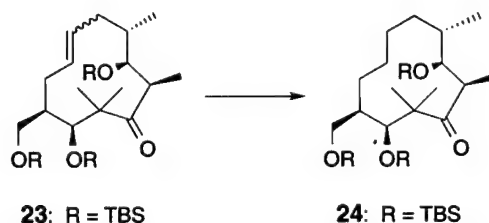
To a solution of alcohol **16** (260 mg, 0.605 mmol) in DCM (2.8 mL) at -78°C was added 2,6-lutidine (332 μL , 2.85 mmol) followed by TBSOTf (288 μL , 1.25 mmol) dropwise. The reaction was allowed to continue with gradual warming to room temperature over three hours before extracting between aqueous pH 7 phosphate buffer and diethyl ether. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo*, and the residue purified by flash column chromatography using 5% ethyl acetate-petroleum ether to give the desired TBS ether adduct **17** (303 mg, 92%): ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, 2H, $J = 8.6$ Hz), 6.85 (d, 2H, $J = 8.6$ Hz), 5.73-5.81 (m, 1H), 5.46-5.54 (m, 1H), 5.45 (s, 1H), 5.05-5.12 (m, 2H), 4.84-4.89 (m, 2H), 4.28 (d, 1H, $J = 2.0$ Hz), 4.21-4.23 (m, 1H), 3.86-3.88 (m, 1H), 3.77-3.80 (m, 1H), 3.78 (s, 3H), 3.26 (quin, 1H, $J = 6.9$ Hz), 2.55-2.62 (m, 1H), 2.33-2.35 (m, 1H), 2.08-2.13 (m, 1H), 1.65-1.74 (m, 2H), 1.33-1.39 (m, 1H), 1.31 (s, 3H), 1.22 (s, 3H), 1.06 (d, 3H, $J = 6.9$ Hz), 0.048 (s, 3H), 0.036 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.4, 160.0, 137.8, 136.6, 131.3, 127.5, 117.0, 115.4, 113.5, 102.4, 83.6, 77.6, 70.5, 55.2, 51.8, 44.9, 38.2, 35.6, 35.4, 30.1, 26.2, 22.1, 21.9, 18.5, 17.6, 16.3, -3.6, -3.7; IR (neat) 1695, 1639, 1616, 1517, 1249 cm^{-1} ; HRMS calculated for $\text{C}_{32}\text{H}_{52}\text{O}_5\text{Si}$ $[\text{M} + \text{H}]^+$ 545.3662, found 545.3674; $[\alpha]_{\text{D}}^{20} -17.6^\circ$ (c 1.0, CHCl_3).

Preparation of **18**:



To a solution of TBS ether **17** (60 mg, 0.110 mmol) in DCM (220 mL) was added $\text{Ti}(\text{O}i\text{Pr})_4$ (10 μL , 0.0331 mmol, freshly fractionally distilled *in vacuo*) and the solution allowed to reflux for one hour before adding a solution of bis(tricyclohexylphosphine)benzylidenerutheniumdichloride (9 mg, 0.0110 mmol) in DCM (9 mL). The reaction was allowed to continue at reflux for seven hours before allowing to cool to room temperature. The solution was then concentrated *in vacuo* and the residue purified by flash column chromatography using 5% ethyl acetate-petroleum ether to give the desired eleven-membered metathesis product **22** (38 mg, 67%) as a 1.9:1 mixture of double bond isomers: ^1H NMR (500 MHz, CDCl_3) δ 7.54 (d, 0.68H, $J = 8.7$ Hz), 7.46 (d, 1.32H, $J = 8.7$ Hz), 6.90 (d, 0.68H, $J = 8.7$ Hz), 6.88 (d, 1.32H, $J = 8.7$ Hz), 5.62-5.66 (m, 0.66H), 5.49-5.53 (m, 0.66H), 5.42 (s, 0.66H), 5.38 (s, 0.34H), 5.24-5.29 (m, 0.34H), 5.15-5.20 (m, 0.34H), 4.31-4.32 (m, 0.34H), 3.97-4.12 (m, 2.66H), 3.79 (s, 1.02H), 3.79 (s, 1.98H), 3.58 (d, 0.66H, $J = 1.9$ Hz), 3.49-3.50 (m, 0.34H), 3.40 (dq, 0.66H, $J = 6.9, 3.7$ Hz), 2.94 (dq, 0.34H, $J = 7.4, 2.6$ Hz), 2.71-2.78 (m, 0.34H), 2.34-2.46 (m, 1.66H), 1.99-2.13 (m, 2.66H), 1.84-1.85 (m, 0.66H), 1.77-1.79 (m, 0.34H), 1.66 (dt, 0.34H, $J = 10.6, 14.1$ Hz), 1.35 (s, 3H), 1.29 (s, 1.02H), 1.27 (s, 1.98H), 1.04 (d, 1.02H, $J = 6.2$ Hz), 1.03 (d, 1.98H, $J = 6.9$ Hz), 0.92 (d, 1.98H, $J = 6.3$ Hz), 0.89 (s, 5.94H), 0.85-0.89 (m, 1.02H), 0.88 (s, 3.06H), 0.12 (s, 3.96H), 0.10 (s, 1.02H), 0.10 (s, 1.02H); IR (neat) 1700, 1616, 1517, 1249 cm^{-1} ; HRMS calculated for $\text{C}_{30}\text{H}_{47}\text{O}_5$ Si $[\text{M} + \text{Na}]^+$ 539.3169, found 539.3160.

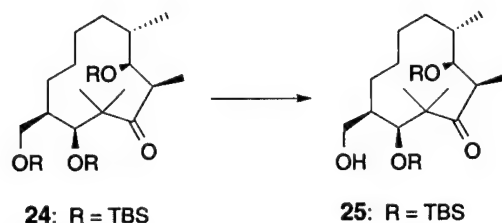
Preparation of **23**:



A solution of the mixture of cis and trans alkenes **23** (29 mg, 0.0463 mmol) in methanol/ethyl acetate (10:1, 1 mL MeOH:0.1 mL EtOAc) was purged with argon for ten minutes. Next, 10% Pd/C (5 mg) was added and the mixture further purged with hydrogen gas before allowing to continue stirring under an atmosphere of hydrogen for four hours. The mixture was then filtered through celite, washing with ethyl acetate, and concentrated *in vacuo*. The residue was purified by column chromatography using a gradient of 1% to 10% ethyl acetate-petroleum ether to give the desired saturated eleven-membered ring **24** (25 mg, 86%): ^1H NMR (500 MHz, CDCl_3) δ 3.95 (dd, 1H, $J = 0, 8.4$ Hz), 3.58 (d, 1H, $J = 2.9$ Hz), 3.43-3.51 (m, 2H), 3.18 (pent, 1H, $J = 6.9$ Hz), 1.95-2.01 (m, 1H), 1.62-1.68 (m, 1H), 1.39-1.58 (m, 5H), 1.30 (s, 3H), 1.24-1.27 (m, 1H), 1.17 (m, 3H), 1.12-1.15 (m, 2H), 1.05 (d, 3H, $J = 6.9$ Hz), 0.93 (s, 9H), 0.88 (s, 9H), 0.88 (s, 9H), 0.87-0.88 (m, 3H), 0.070 (s, 3H), 0.054 (s, 3H), 0.041 (s, 3H), 0.034 (s, 6H), 0.0030 (s,

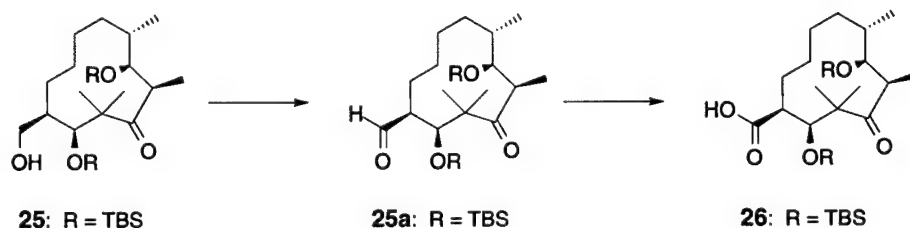
3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 216.2, 80.5, 78.1, 64.8, 52.6, 48.0, 42.9, 36.0, 30.4, 29.4, 26.2, 26.2, 26.1, 26.0, 25.1, 25.1, 23.4, 18.9, 18.7, 18.5, 18.3, 17.9, -3.2, -3.6, -3.7, -4.2, -5.2, -5.3; IR (neat) 1694, 1472, 1463, 1255, 1100, 835, 773 cm^{-1} ; HRMS calculated for $\text{C}_{34}\text{H}_{72}\text{O}_4\text{Si}_3$ $[\text{M} + \text{H}]^+$: 629.4817; found: 629.4798.

Preparation of **25**:



To a solution of the tri-TBS **24** (9 mg, 0.0143 mmol) in methanol (0.3 mL) at 0 °C was added catalytic PPTS and the reaction allowed to continue stirring at this temperature while monitoring by TLC. After four hours the reaction was warmed to room temperature and allowed to continue stirring at this temperature overnight. Although TLC analysis showed the reaction was not complete, the reaction was worked up after approx. 24 hours. The reaction mixture was extracted between aqueous pH 7 phosphate buffer and ethyl acetate. The combined organic layers were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 4% to 10% ethyl acetate-petroleum ether to give the desired primary hydroxyl **25** (3 mg, 41%, 92% based on recovered starting material): ^1H NMR (500 MHz, CDCl_3) δ 3.95 (dd, 1H, J = 1.1, 8.5 Hz), 3.60 (d, 1H, J = 2.9 Hz), 3.53-3.60 (m, 2H), 3.20 (dq, 1H, J = 6.9, 13.9 Hz), 2.02-2.05 (m, 1H), 1.55-1.66 (m, 2H), 1.40-1.50 (m, 3H), 1.33 (s, 3H), 1.11-1.29 (m, 5H), 1.19 (s, 3H), 1.06 (d, 3H, J = 6.9 Hz), 0.93 (s, 9H), 0.88 (s, 9H), 0.87-0.88 (m, 3H), 0.11 (s, 3H), 0.057 (s, 3H), 0.044 (s, 3H), 0.024 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 216.0, 81.1, 78.2, 64.6, 52.4, 48.0, 42.9, 35.6, 30.0, 29.5, 26.2, 26.2, 25.6, 25.2, 24.8, 23.3, 18.8, 18.7, 18.5, 18.0, -3.4, -3.6, -3.7, -3.9; IR (neat) 3482, 1693, 1472, 1253, 836, 773 cm^{-1} ; HRMS calculated for $\text{C}_{28}\text{H}_{58}\text{O}_4\text{Si}_2$ $[\text{M} + \text{H}]^+$ 515.3952, found 515.3967; $[\alpha]_D^{20}$ -8.4 ° (c 0.5, CHCl_3).

Preparation of **26**:

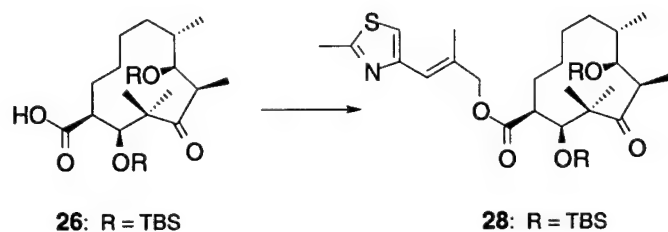


To a solution of primary hydroxyl **25** (10 mg, 0.0195 mmol) in DMF (0.43 mL) at room temperature was added PDC (81 mg, 0.214 mmol) and the reaction allowed to stir vigorously for four hours. The mixture was then extracted between distilled water (4.0 mL) and diethyl ether. The combined organic extracts were then dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography to provide the aldehyde **25a** (10 mg, 100%): ^1H NMR (500 MHz, CDCl_3) δ 9.66 (d, 1H, J = 2.2 Hz), 3.91-3.93 (m, 2H), 3.19 (dq, 1H, J = 6.8, 9.2 Hz), 3.01-3.06 (m, 1H), 1.69-1.76 (m, 2H), 1.55-1.63 (m, 3H), 1.46-1.51 (m, 1H), 1.26-1.41 (m, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 1.03 (d, 3H, J = 6.7 Hz),

0.93 (s, 9H), 0.90 (d, 3H, $J = 6.8$ Hz), 0.88 (s, 9H), 0.11 (s, 3H), 0.064 (s, 3H), 0.041 (s, 3H), -0.034 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.0, 202.7, 79.0, 76.7, 53.6, 53.3, 48.8, 35.4, 29.7, 27.4, 26.3, 26.0, 25.3, 25.3, 25.0, 22.6, 19.2, 18.6, 18.4, 17.9, -3.2, -3.4, -3.6, -4.3; IR (neat) 1725, 1695, 1473, 1256, 1106, 836, 774 cm^{-1} ; HRMS calculated for $\text{C}_{28}\text{H}_{56}\text{O}_4\text{Si}_2$ $[\text{M} + \text{Na}]^+$ 535.3615, found 535.3627; $[\alpha]_{\text{D}}^{20}$ 14.4° (c 0.5, CHCl_3).

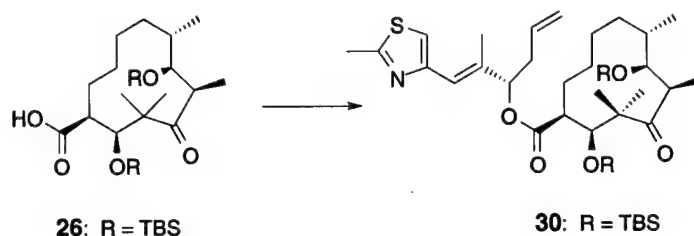
To a solution of aldehyde **25a** (10 mg, 0.0195 mmol) in *t*-BuOH (1.95 mL) and 2-methyl-2-butene (98 mL) was added a solution of NaClO_2 (2.5 mg, 0.0276 mmol) in aqueous pH 3.5 phosphate buffer (0.39 mL) dropwise. The reaction was allowed to stir at room temperature for 30 minutes before extracting between distilled water and diethyl ether. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 10% to 20% ethyl acetate-petroleum ether to give the desired acid **26** (9 mg, 87%): ^1H NMR (500 MHz, CDCl_3) δ 3.94-3.97 (m, 2H), 3.25-3.33 (m, 2H), 1.87-1.94 (m, 1H), 1.72-1.78 (m, 1H), 1.65-1.70 (m, 2H), 1.55-1.61 (m, 2H), 1.38-1.49 (m, 2H), 1.34 (s, 3H), 1.31-1.34 (m, 1H), 1.19 (s, 3H), 1.08 (d, 3H, $J = 6.5$ Hz), 0.99 (s, 9H), 0.95 (d, 3H, $J = 6.9$ Hz), 0.94 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H), 0.092 (s, 3H), 0.080 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.1, 182.2, 78.0, 79.5, 53.9, 49.0, 46.9, 35.2, 30.2, 29.2, 27.3, 26.3, 26.0, 25.5, 25.0, 21.4, 19.2, 18.6, 18.5, 18.0, -3.0, -3.3, -3.5, -4.2; IR (neat) 2500-3300, 1700, 1468, 1255, 1106, 837, 774 cm^{-1} ; HRMS calculated for $\text{C}_{28}\text{H}_{56}\text{O}_5\text{Si}_2$ $[\text{M} + \text{Na}]^+$ 551.3564, found 551.3556; $[\alpha]_{\text{D}}^{20}$ -4.4° (c 0.45, CHCl_3).

Preparation of **28**:



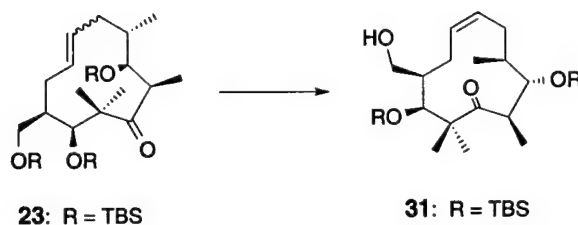
To a solution of acid **26** (5.4 mg, 0.0102 mmol) in methylene chloride (0.3 mL) at room temperature was added DCC (3 mg, 0.0133 mmol) followed by DMAP (2 mg, 0.0133 mmol). To the reaction mixture was then added a solution of thiazole alcohol **27** (2 mg, 0.0123 mmol) in methylene chloride (0.2 mL) and the reaction allowed to continue stirring for 24 hours. The mixture was filtered through celite, washing with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using a gradient of 2% to 10% ethyl acetate-petroleum ether to give the desired ester **28** (6 mg, 87%): ^1H NMR (500 MHz, CDCl_3) δ 6.96 (s, 1H), 6.54 (s, 1H), 4.68 (d, 1H, $J = 37.8$ Hz), 4.65 (d, 1H, $J = 38.3$ Hz), 3.90-3.92 (m, 2H), 3.22-3.27 (m, 2H), 2.70 (s, 3H), 2.13 (s, 3H), 1.81-1.87 (m, 1H), 1.60-1.73 (m, 4H), 1.45-1.50 (m, 1H), 1.35-1.38 (m, 2H), 1.23-1.29 (m, 1H), 1.23 (s, 3H), 1.12 (s, 3H), 1.01 (d, 3H, $J = 6.7$ Hz), 0.93 (s, 9H), 0.88-0.90 (m, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.064 (s, 3H), 0.038 (s, 3H), 0.032 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.2, 176.8, 164.9, 152.4, 134.0, 121.9, 116.6, 80.0, 79.6, 77.2, 77.0, 76.7, 70.6, 53.9, 49.1, 47.2, 35.2, 30.5, 29.2, 27.2, 26.3, 26.1, 25.6, 25.1, 21.3, 19.3, 19.3, 18.6, 18.5, 18.0, 16.2, -2.9, -3.3, -3.5, -4.2; IR (neat) 1734, 1694, 1463, 1255, 1103, 836, 774 cm^{-1} ; HRMS calculated for $\text{C}_{36}\text{H}_{65}\text{NO}_5\text{SSi}_2$ $[\text{M} + \text{Na}]^+$ 702.4020, found 702.4011; $[\alpha]_{\text{D}}^{20}$ -4.3° (c 0.3, CHCl_3).

Preparation of **30**:

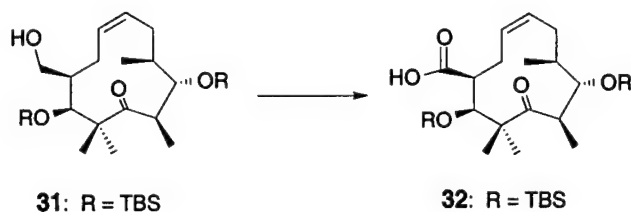


To a solution of acid **26** (4 mg, 0.00760 mmol) in methylene chloride (0.3 mL) at room temperature was added DCC (2 mg, 0.00980 mmol) followed by DMAP (1 mg, 0.00980 mmol). To the reaction mixture was then added a solution of thiazole alcohol **29** (2 mg, 0.00910 mmol) in methylene chloride (0.2 mL) and the reaction allowed to continue stirring for 24 hours. The mixture was filtered through celite, washing with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using a gradient of 2% to 10% ethyl acetate-petroleum ether to give the desired ester **30** (3.7 mg, 66%): ^1H NMR (500 MHz, CDCl_3) δ 6.93 (s, 1H), 6.52 (s, 1H), 5.74 (dddd, 1H, J = 6.4, 6.4, 10.1, 16.8 Hz), 5.30 (dd, 1H, J = 5.7, 7.8 Hz), 5.13 (dd, 1H, J = 1.5, 17.0 Hz), 5.06 (dd, 1H, J = 1.6, 10.1 Hz), 3.89-3.91 (m, 2H), 3.22-3.28 (m, 2H), 2.69 (s, 3H), 2.54-2.60 (m, 1H), 2.45-2.50 (m, 1H), 2.13 (s, 3H), 1.80-1.84 (m, 1H), 1.59-1.72 (m, 3H), 1.23-1.46 (m, 5H), 1.20 (s, 3H), 1.10 (s, 3H), 1.01 (d, 3H, J = 6.7 Hz), 0.92 (s, 9H), 0.90 (s, 9H), 0.90 (d, 3H, J = 4.6 Hz), 0.095 (s, 3H), 0.069 (s, 3H), 0.042 (s, 3H), 0.019 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.4, 175.9, 164.7, 152.5, 136.7, 133.5, 121.3, 118.1, 116.6, 79.9, 79.8, 78.9, 54.1, 49.2, 47.0, 37.8, 34.9, 30.8, 29.0, 27.0, 26.3, 26.1, 25.7, 24.7, 21.5, 19.3, 19.3, 18.6, 18.5, 18.0, 14.6, -2.8, -3.2, -3.5, -4.2; IR (neat) 1733, 1694, 1472, 1256, 1104, 836, 774 cm^{-1} ; HRMS calculated for $\text{C}_{39}\text{H}_{69}\text{NO}_5\text{SSi}_2$ $[\text{M} + \text{Na}]^+$ 742.4333, found 742.4330; $[\alpha]_{\text{D}}^{20}$ -5.9° (c 0.18, CHCl_3).

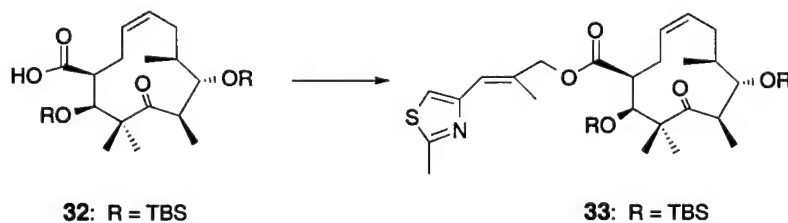
Preparation of **31**:



To a solution of trisilyl **23** (58 mg, 0.0927 mmol) in DCM/MeOH (0.6 mL : 0.3 mL) at 0 °C was added camphorsulphonic acid (4 mg, 0.0185 mmol) and the reaction stored at -5 °C for twenty two hours. The reaction was quenched by the addition of solid NaHCO_3 and the mixture was then extracted between aqueous pH 7 phosphate buffer and ethyl acetate. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 10% to 30% ethyl acetate-petroleum ether to give the desired primary hydroxyl **31** (15 mg, 32%) as a single olefin isomer (assigned as *cis* based on its 10.7 Hz coupling constant): ^1H NMR (500 MHz, CDCl_3) δ 5.55-5.60 (m, 1H), 5.45-5.50 (m, 1H), 3.98 (d, 1H, J = 4.6 Hz), 3.64 (s, 1H), 3.49-3.59 (m, 2H), 3.19 (dq, 1H, J = 6.8, 6.8 Hz), 2.15-2.24 (m, 2H), 2.03-2.09 (m, 2H), 1.94-2.01 (m, 1H), 1.51-1.54 (m, 1H), 1.40-1.45 (m, 1H), 1.28 (s, 3H), 1.14 (s, 3H), 1.06 (d, 3H, J = 6.9 Hz), 0.93 (s, 9H), 0.90 (d, 3H, J = 6.5 Hz), 0.88 (s, 9H), 0.11 (s, 3H), 0.082 (s, 3H), 0.064 (s, 3H), 0.050 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 216.8, 130.8, 128.6, 79.4, 77.8, 65.6, 52.7, 46.6, 44.1, 37.2, 30.0, 29.7, 27.0, 26.2, 26.1, 25.0, 18.6, 18.4, 16.4, 16.0, -3.3, -3.9, -4.0, -4.3; IR (neat) 3438, 1694, 1471, 1253, 835 cm^{-1} ; $[\alpha]_{\text{D}}^{20}$ 11.9° (c 0.75, CHCl_3).

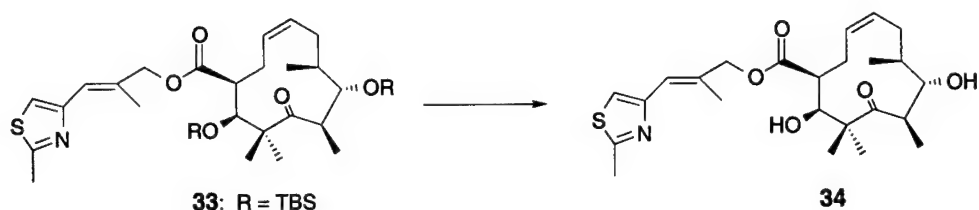
Preparation of **32**:

To a solution of primary alcohol **31** (15 mg, 0.0293 mmol) in DMF (0.242 mL) was added PDC (121 mg, 0.322 mmol) and the reaction stirred vigorously for two days. The reaction mixture was then poured into 2.1 mL water and extracted with diethyl ether. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 10% to 20% ethyl acetate-petroleum ether to give the desired acid **32** (10 mg, 65%): ^1H NMR (500 MHz, CDCl_3) δ 5.53-5.61 (m, 2H), 4.01 (s, 1H), 3.96 (d, 1H, $J = 5.0$ Hz), 3.16 (dq, 1H, $J = 6.7, 6.7$ Hz), 3.00-3.02 (m, 1H), 2.26-2.35 (m, 1H), 2.15-2.24 (m, 1H), 2.01-2.09 (m, 2H), 1.93-1.97 (m, 1H), 1.32 (s, 3H), 1.18 (s, 3H), 1.06 (d, 3H, $J = 6.9$ Hz), 0.93 (s, 9H), 0.91 (d, 3H, $J = 6.6$ Hz), 0.88 (s, 9H), 0.093 (s, 3H), 0.079 (s, 3H), 0.062 (s, 3H), -0.014 (s, 3H); IR (neat) 2500-3300 (br), 1701, 1253, 1114, 835 cm^{-1} ; $[\alpha]_{\text{D}}^{20}$ -10.2° (c 0.50, CHCl_3).

Preparation of **33**:

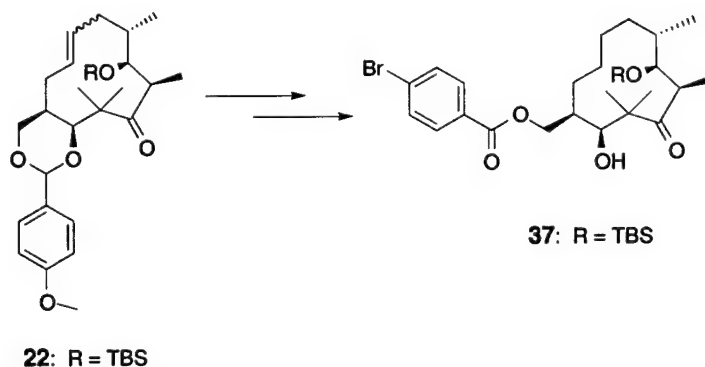
To a solution of acid **32** (10 mg, 0.019 mmol) in methylene chloride (0.36 mL) at room temperature was added DCC (5 mg, 0.0247 mmol) followed by DMAP (3 mg, 0.0247 mmol). To the reaction mixture was then added a solution of thiazole alcohol **27** (4 mg, 0.0228 mmol) in methylene chloride (0.5 mL) and the reaction allowed to continue stirring for two hours. The mixture was filtered through celite, washing with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using a gradient of 5% to 10% ethyl acetate-petroleum ether to give the desired ester **33** (7 mg, 54%): ^1H NMR (500 MHz, CDCl_3) δ 6.95 (s, 1H), 6.51 (s, 1H), 5.53-5.62 (m, 2H), 4.64 (s, 2H), 3.97 (d, 1H, $J = 2.2$ Hz), 3.92 (dd, 2H, $J = 1.5, 6.0$ Hz), 3.15 (dq, 1H, $J = 6.8, 6.8$ Hz), 3.06-3.08 (m, 1H), 2.70 (s, 3H), 2.38-2.43 (m, 1H), 2.03-2.15 (m, 6H), 1.90-1.95 (m, 1H), 1.33 (s, 3H), 1.18 (s, 3H), 1.06 (d, 3H, $J = 6.8$ Hz), 0.92 (s, 9H), 0.90 (d, 3H, $J = 6.8$ Hz), 0.88 (s, 9H), 0.075 (s, 3H), 0.063 (s, 3H), 0.060 (s, 3H), -0.097 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 216.0, 175.3, 164.8, 152.4, 134.0, 130.1, 128.7, 121.6, 116.5, 80.3, 78.1, 70.7, 52.7, 47.3, 46.4, 36.6, 29.5, 26.4, 26.2, 26.1, 25.9, 24.4, 23.5, 19.2, 18.5, 18.4, 16.8, 16.2, -3.8, -3.8, -3.9, -4.9; IR (neat) 1733, 1696, 1462, 1252, 1115, 836 cm^{-1} ; HRMS calculated for $\text{C}_{36}\text{H}_{63}\text{NO}_5\text{SSi}_2$ $[\text{M} + \text{Na}]^+$ 700.3863, found 700.3872; $[\alpha]_{\text{D}}^{20}$ -28.4° (c 0.50, CHCl_3).

Preparation of **34**:



To a solution of di-TBS ether **33** (7 mg, 0.010 mmol) in DCM (0.5 mL) at 0 °C was added TFA (0.1 mL) dropwise and the reaction allowed to stir at this temperature for two hours at which time an additional portion of DCM (0.2 mL) and TFA (0.05 mL) were added in hopes of pushing the reaction further to completion. After thirty minutes the reaction mixture was poured into a cold saturated aqueous solution of NaHCO₃ and the aqueous layer extracted with chloroform. The combined organic extracts were dried (MgSO₄), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 20% to 40% ethyl acetate-petroleum ether to give the desired diol **34** (3 mg, 63%): ¹H NMR (500 MHz, CDCl₃) δ 6.94 (s, 1H), 6.49 (s, 1H), 5.61-5.70 (m, 2H), 4.66 (dd, 2H, *J* = 13.0, 16.0 Hz), 4.05 (d, 1H, *J* = 9.6 Hz), 3.92 (dd, 1H, *J* = 1.2, 9.5 Hz), 3.80-3.82 (m, 1H), 3.31 (dq, 1H, *J* = 6.9, 6.9 Hz), 2.81-2.83 (m, 1H), 2.69 (s, 3H), 2.35-2.41 (m, 1H), 2.15-2.24 (m, 2H), 2.08 (s, 3H), 1.94-1.99 (m, 1H), 1.80-1.85 (m, 1H), 1.50-1.62 (m, 1H), 1.44 (s, 3H), 1.40 (s, 3H), 1.27 (d, 3H, *J* = 6.9 Hz), 0.99 (d, 3H, *J* = 6.8 Hz); ¹³C NMR (125.7 MHz, CDCl₃) δ 225.4, 174.3, 164.8, 152.4, 134.2, 131.0, 129.1, 121.4, 116.4, 82.3, 77.9, 70.6, 50.1, 47.6, 47.5, 34.1, 29.7, 28.0, 22.8, 22.7, 19.2, 17.5, 16.7, 16.1; IR (neat) 3486, 1733, 1670, 1455, 1175, 975 cm⁻¹; HRMS calculated for C₂₄H₃₅NO₅S [M + Na]⁺ 472.2134, found 472.2131; [α]_D²⁰ -62.7 ° (c 0.14, CHCl₃).

Preparation of **37**:

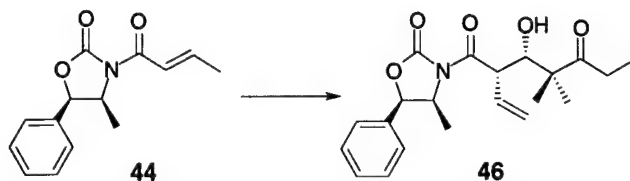


After hydrolysis of the benzylidene acetal (as described above for the preparation of trisilyl ether), the resulting diol **35** (29 mg, 0.07 mmol), as a mixture of *cis* and *trans* isomers, was dissolved in methanol/ethyl acetate (10:1, 2 mL methanol: 0.2 mL ethyl acetate) and the solution purged with argon for ten minutes. Next, 10% Pd/C (5 mg) was added and the mixture was purged with hydrogen gas and allowed to continue stirring under an atmosphere of hydrogen for 18 hours. The mixture was then filtered through celite, washing with ethyl acetate, and concentrated *in vacuo*. The resulting white solid (27 mg, 93%) was carried on without further purification.

To a solution of **36** prepared above (28 mg, 0.07 mmol) in dichloromethane (0.7 mL) at 0 °C was added pyridine (17 μL, 0.21 mmol) followed by *p*-bromobenzoyl chloride (38 mg, 0.18 mmol) and catalytic DMAP. The reaction was allowed to warm to room temperature with stirring for 24 hours before diluting

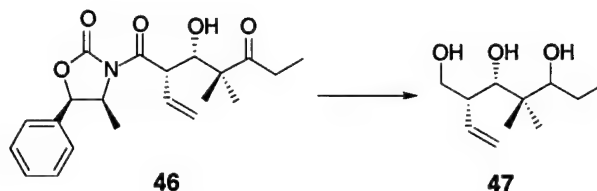
the reaction mixture with ethyl acetate and washing with water followed by saturated aqueous sodium bicarbonate. The organic extract was dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient 10% to 40% ethyl acetate-petroleum ether to give the desired ester **37** (10 mg, 24%; 69% based on recovered starting material): ^1H NMR (500 MHz, CDCl_3): δ 7.83-7.87 (m, 2H), 7.53-7.57 (m, 2H), 4.32 (dd, 1H, $J = 5.6, 10.7$ Hz), 4.24 (dd, 1H, $J = 8.8, 10.6$ Hz), 4.10 (d, 1H, $J = 9.0$ Hz), 3.97 (dd, 1H, $J = 2.2, 7.3$ Hz), 3.53 (dd, 1H, $J = 1.4, 9.1$ Hz), 3.21 (quintet, 1H, $J = 7.1$ Hz), 2.02-2.04 (m, 1H), 1.51-1.70 (m, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.22-1.30 (m, 3H), 1.14 (d, 3H, $J = 7.1$ Hz), 1.02-1.12 (m, 3H), 0.89 (d, 3H, $J = 6.5$ Hz), 0.88 (s, 9H), 0.077 (s, 3H), 0.070 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3): δ 224.9, 165.7, 131.7, 131.0, 129.3, 128.0, 82.8, 76.1, 66.8, 49.2, 46.0, 40.7, 37.2, 30.2, 30.0, 29.7, 26.9, 26.8, 26.1, 22.4, 18.4, 17.6, 17.1, -3.8, -3.9; IR (neat): 3456, 1721, 1670, 1590, 1462, 1270 cm^{-1} ; HRMS calculated for $\text{C}_{29}\text{H}_{47}\text{BrO}_5\text{Si}$ $[\text{M} + \text{Na}]^+$ 605.2274; found: 605.2264; $[\alpha]_{\text{D}}^{20} +12.9^\circ$ (c 0.45, CHCl_3).

Preparation of **46**:



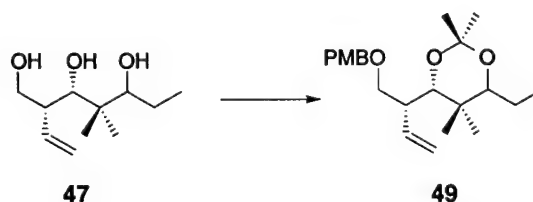
To a solution of oxazolidinone **44** (24.567 g, 100 mmol) in methylene chloride (143 mL) at -78°C was added triethylamine (16.971 mL, 122 mmol, freshly fractionally distilled under Ar from calcium hydride) dropwise over twenty minutes. Next, dibutylborontriflate (93.11 mL, 1.0 M solution in methylene chloride, 93.1 mmol) was added dropwise over one hour and the resulting homogeneous pale yellow solution was allowed to continue stirring at -78°C for 30 minutes before gradually warming to 0°C , stirring at that temperature for twenty minutes, and recooling to -78°C . Next, a solution of aldehyde **45** (9.168 g, 71.6 mmol) was added dropwise via cannula and the reaction allowed to continue stirring at -78°C for fifteen hours before warming to 0°C and stirring at that temperature for five hours. The reaction was then quenched by the addition of aqueous pH 7 phosphate buffer (124 mL) followed by MeOH (370 mL). Next, the reaction was treated with a solution of H_2O_2 : MeOH (123 mL : 123 mL) over 40 minutes. The biphasic mixture was allowed to continue stirring at 0°C for 30 minutes and then warmed to room temperature and stirred for an additional 30 minutes before concentrating *in vacuo*. The resulting residue was diluted with 10 % aqueous sodium bicarbonate and the aqueous layer washed with methylene chloride. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 1% to 2% diethyl ether-methylene chloride to give the desired aldol adduct **46** (11.320 g, 42%; 53% based on recovered acylated oxazolidinone **171**) in 71% diastereomeric excess. Spectroscopic data shown is for the major (desired) diastereomer only: ^1H NMR (500 MHz, CDCl_3) δ 7.34-7.39 (m, 3H), 7.28 (d, 2H, $J = 7.1$ Hz), 5.97 (ddd, 1H, $J = 9.9, 9.9, 17.3$ Hz), 5.70 (d, 1H, $J = 7.2$ Hz), 5.29 (dd, 1H, $J = 1.2, 17.2$ Hz), 5.24 (dd, 1H, $J = 1.4, 10.2$ Hz), 4.71-4.73 (m, 2H), 4.14 (dd, 1H, $J = 4.0, 6.2$ Hz), 3.84 (d, 1H, $J = 6.3$ Hz), 2.52 (q, 2H, $J = 7.1$ Hz), 1.26 (s, 3H), 1.20 (s, 3H), 0.98 (t, 3H, $J = 7.1$ Hz), 0.84 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.2, 172.8, 152.7, 133.1, 132.8, 128.8, 128.7, 125.6, 120.1, 79.0, 77.3, 55.1, 50.6, 50.4, 32.1, 23.3, 21.0, 14.1, 7.5; IR (neat) 3504, 2975, 1780, 1696, 1350, 1196, 1119 cm^{-1} ; HRMS calculated for $\text{C}_{21}\text{H}_{27}\text{NO}_5$ $[\text{M} + \text{Na}]^+$ 396.1787, found 396.1792; $[\alpha]_{\text{D}}^{20} -62.3^\circ$ (c 1.0, CHCl_3).

Preparation of **47**:



To a solution of aldol adduct **46** (4.0 g, 10.7 mmol) in THF (35 mL) was added glacial acetic acid (2.368 mL) followed by tributylborane (13.084 mL, 1.0 M solution in THF, 13.1 mmol). The mixture was allowed to stir for one and one half hours before cooling to 0 °C and adding lithium borohydride (21.448 mL, 2.0 M solution in THF, 42.9 mmol) dropwise. The reaction was allowed to continue stirring at this temperature for one and one half hours before warming to room temperature and stirring for an additional hour. The reaction was then cooled to 0 °C and quenched by the addition of MeOH (83 mL) followed by aqueous pH 7 phosphate buffer (40 mL). Next, a solution of H₂O₂ (20 mL) in MeOH (40 mL) was added before warming to room temperature and stirring at this temperature for one and one half hours. The volatile components were then removed *in vacuo*, and the remaining residue was diluted with aqueous sodium bicarbonate and washed with methylene chloride. The combined organic extracts were dried (MgSO₄), concentrated *in vacuo* and the resulting mixture of product and auxiliary was taken up in diethyl ether and petroleum ether. The solution was then stored at -5 °C overnight in order to precipitate the chiral auxiliary. In the morning, the solution was decanted, the remaining solid washed with cold diethyl ether and the solution of the triol product (still as its boron complex) concentrated *in vacuo*. The resulting residue was then diluted with THF (30 mL) and allowed to stir with a solution of 2 M aqueous sodium hydroxide (30 mL) for four hours. The THF was then removed *in vacuo*, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were then dried (MgSO₄), concentrated *in vacuo* and the residue was purified by flash column chromatography using a gradient of 10% to 60% ethyl acetate-chloroform to provide the desired triol **47** (1.473 g, 68%). Spectroscopic data shown is for the major isomer only: ¹H NMR (500 MHz, CDCl₃) δ 6.03 (ddd, 1H, *J* = 10.2, 10.2, 17.5 Hz), 5.10 (dd, 1H, *J* = 1.9, 10.4 Hz), 5.06 (dd, 1H, *J* = 1.8, 17.5 Hz), 4.27 (br s, 1H), 3.79 (s, 1H), 3.74-3.77 (m, 1H), 3.60-3.61 (m, 2H), 3.46 (br s, 1H), 3.30 (d, 1H, *J* = 9.8 Hz), 2.45-2.49 (m, 1H), 1.48-1.56 (m, 1H), 1.22-1.28 (m, 1H), 0.92 (t, 3H, *J* = 7.3 Hz), 0.86 (s, 3H), 0.73 (s, 3H); ¹³C NMR (125.7 MHz, CDCl₃) δ 136.5, 117.1, 83.0, 79.5, 66.8, 47.3, 41.5, 24.1, 21.0, 15.1, 11.1; IR (neat) 3360, 2972, 1877, 1468, 1100, 1047 cm⁻¹; HRMS calculated for C₁₁H₂₂O₃ [M + Na]⁺ 225.1467, found 225.1472.

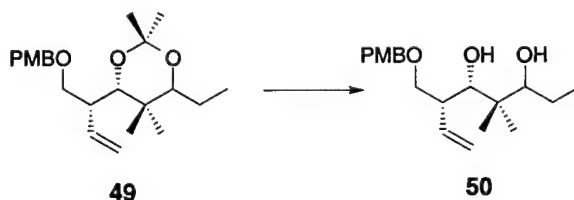
Preparation of **49**:



To a solution of triol **47** (980 mg, 4.85 mmol) in acetone (50 mL) was added copper sulfate (3.871 g, 242 mmol) followed by pyridinium *p*-toluenesulfonate (PpTS) (122 mg, 0.485 mmol) and the reaction allowed to continue stirring for five days. (For reaction times shorter than this, the desired acetonide was accompanied by the undesired kinetic acetonide involving the primary hydroxyl.) The mixture was then

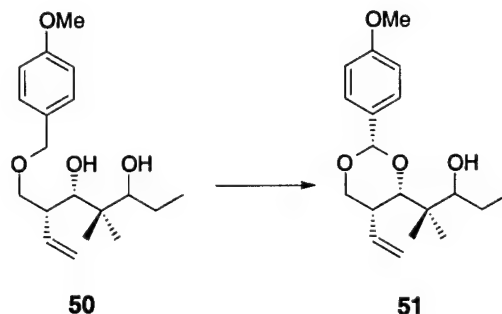
filtered through a pad of celite, washing liberally with methylene chloride. The organic solution was washed with saturated aqueous sodium bicarbonate followed by brine. The organic layer was dried (MgSO_4) and concentrated *in vacuo* to provide acetonide **48** (1.098 g, 93%). (This acetonide was used directly without further purification.) A solution of the acetonide **48** (1.202 g, 4.97 mmol) in THF (11 mL) was then added dropwise to a solution of sodium hydride (397 mg, 9.93 mmol) in dimethylformamide (11 mL) at 0 °C. The reaction was allowed to stir at this temperature for 30 minutes before adding *p*-methoxybenzoylchloride (PMBCl) (1.347 mL, 9.93 mmol) and warming to room temperature. After stirring for approximately 12 hours, an additional portion of sodium hydride (176 mg, 4.97 mmol) and PMBCl (0.5 mL) were added before quenching the reaction by the addition of ice cold water and extracting with diethyl ether. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 2% to 5% ethyl acetate-1% triethylamine-petroleum ether to provide the desired PMB ether **49** (1.313 g, 73%). Spectroscopic data shown is for the major isomer only: ^1H NMR (500 MHz, CDCl_3) δ 7.23 (d, 2H, $J = 9.0$ Hz), 6.85 (d, 2H, $J = 8.6$ Hz), 5.95 (ddd, 1H, $J = 8.9, 10.4, 19.3$ Hz), 5.00-5.05 (m, 2H), 4.42 (d, 1H, $J = 32.2$ Hz), 4.40 (d, 1H, $J = 32.2$ Hz), 3.79 (s, 3H), 3.74 (s, 1H), 3.42 (t, 1H, $J = 18.6$ Hz), 3.25 (dd, 1H, $J = 1.6, 10.0$ Hz), 3.18 (dd, 1H, $J = 5.5, 9.1$ Hz), 2.63-2.68 (m, 1H), 1.40-1.48 (m, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.17-1.27 (m, 1H), 0.88 (t, 3H, $J = 7.3$ Hz), 0.85 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 159.3, 137.2, 130.7, 129.2, 116.2, 113.7, 98.5, 81.0, 75.7, 72.7, 72.6, 55.3, 43.8, 36.8, 30.0, 21.7, 20.9, 19.4, 14.6, 11.4; IR (neat) 2963, 1935, 2874, 1613, 1513, 1465, 1377, 1248, 1177, 1115, 1094, 1036 cm^{-1} ; HRMS calculated for $\text{C}_{22}\text{H}_{34}\text{O}_4$ $[\text{M}]^+$ 362.2457, found 362.2441.

Preparation of **50**:



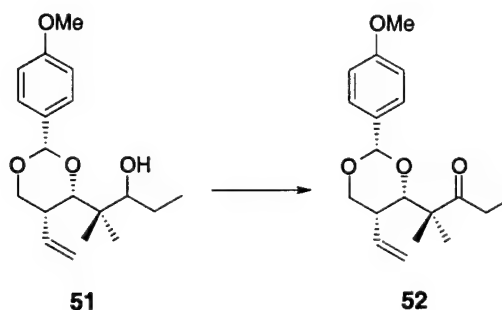
PMB ether **49** (1.195 g, 3.30 mmol) was dissolved in 80% glacial acetic acid/water (21 mL) and the solution allowed to stir at room temperature for three and one half days before concentrating and purifying by flash column chromatography using a gradient of 4% to 20% ethyl acetate-petroleum ether to provide the desired diol **50** (895 mg, 84%, 94% based on recovered starting material). Spectroscopic data shown is for the major isomer only: ^1H NMR (500 MHz, CDCl_3) δ 7.21 (d, 2H, $J = 8.4$ Hz), 6.5 (d, 2H, $J = 8.6$ Hz), 6.11 (ddd, 1H, $J = 9.3, 10.4, 19.5$ Hz), 5.07-5.13 (m, 2H), 4.42 (s, 1H), 3.78 (s, 3H), 3.51-3.58 (m, 2H), 3.47 (m, 2H), 3.35 (dd, 1H, $J = 1.5, 10.2$ Hz), 2.60-2.64 (m, 1H), 1.44-1.56 (m, 1H), 1.22-1.30 (m, 1H), 0.96 (t, 3H, $J = 7.3$ Hz), 0.89 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 159.3, 136.7, 129.9, 129.2, 116.8, 113.8, 82.3, 80.2, 75.6, 73.1, 55.2, 45.2, 41.6, 24.1, 21.0, 15.4, 11.3; IR (neat) 3424, 2968, 2934, 2874, 1612, 1513, 1248, 1090 cm^{-1} ; HRMS calculated for $\text{C}_{19}\text{H}_{30}\text{O}_4$ $[\text{M} + \text{Na}]^+$ 345.2042, found 345.2029.

Preparation of **51**:



To a solution of diol **50** (217 mg, 0.674 mmol) in methylene chloride (5 mL) was added dichlorodicyanoquinone (168 mg, 0.741 mmol) and the reaction allowed to stir for several hours until thin layer chromatography analysis suggested that the reaction was complete. The reaction mixture was then extracted between methylene chloride and 0.5 M aqueous sodium hydroxide. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the resulting residue purified by flash column chromatography with 20% ethyl acetate-petroleum ether to give the desired cyclic benzylidene acetal **51** (144 mg, 67%): ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.41 (m, 2H), 6.85-6.88 (m, 2H), 6.50-6.57 (m, 0.18H), 6.43-6.51 (m, 0.82H), 5.57 (s, 0.82H), 5.50 (s, 0.18H), 5.09-5.15 (m, 2H), 4.14 (dd, 0.82H, $J = 2.4, 10.9$ Hz), 4.09-4.13 (m, 0.18H), 4.02-4.04 (m, 0.18H), 4.01 (dd, 0.82H, $J = 1.5, 10.8$ Hz), 3.94 (d, 0.18H, $J = 1.9$ Hz), 3.93 (d, 0.82H, $J = 1.9$ Hz), 3.78 (s, 0.54H), 3.77 (s, 2.46H), 3.36-3.38 (m, 0.82H), 3.23-3.26 (m, 0.18H), 2.89-2.90 (m, 0.18H), 2.80 (s, 0.82H), 2.33-2.35 (m, 0.82H), 2.25-2.27 (m, 0.18H), 1.44-1.58 (m, 1H), 1.22-1.32 (m, 1H), 0.95-0.99 (m, 3H), 0.97 (s, 2.46H), 0.93 (s, 0.54H), 0.85 (s, 2.46H), 0.81 (s, 0.54H); ^{13}C NMR (125.7 MHz, CDCl_3 , major isomer only) δ 159.9, 138.6, 131.0, 127.3, 115.4, 113.6, 102.1, 86.4, 81.4, 75.3, 55.2, 42.0, 41.6, 24.2, 19.8, 16.7, 11.2; IR (neat) 3471, 2966, 2934, 2874, 2839, 1615, 1518, 1249, 1117, 1036, 830 cm^{-1} ; HRMS calculated for $\text{C}_{19}\text{H}_{28}\text{O}_4$ $[\text{M} + \text{H}]^+$ 321.2066, found 321.2064.

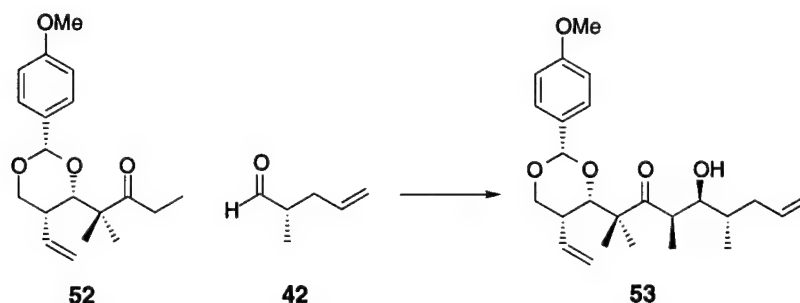
Preparation of **52**:



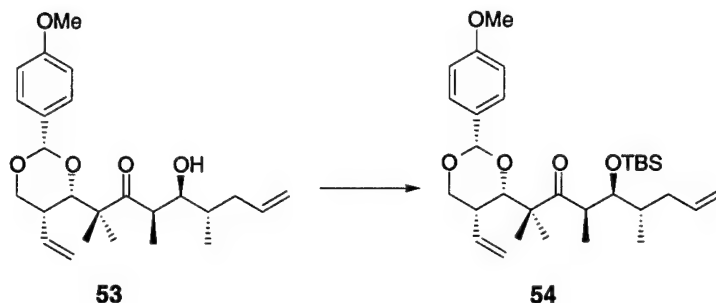
To a solution of alcohol **51** (459 mg, 1.43 mmol) in methylene chloride (8 mL) was added Dess-Martin periodinane reagent (1.219 g, 2.87 mmol) and the reaction allowed to continue stirring for two hours before extracting between methylene chloride and 2 M aqueous sodium hydroxide. The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue purified by flash column chromatography with a gradient of 5% to 10% ethyl acetate-petroleum ether to provide the desired ethyl ketone **52** (421 mg, 92%): ^1H NMR (500 MHz, CDCl_3) δ 7.38 (d, 2H, $J = 8.7$ Hz), 6.88 (d, 2H, $J = 8.8$

Hz), 6.36 (ddd, 1H, $J = 10.2, 10.2, 17.2$ Hz), 5.51 (s, 1H), 5.10 (dd, 1H, $J = 1.8, 10.4$ Hz), 5.08 (dd, 1H, $J = 1.7, 17.3$ Hz), 4.14 (dd, 1H, $J = 2.5, 11.0$ Hz), 4.12 (d, 1H, $J = 2.1$ Hz), 4.01 (dd, 1H, $J = 1.6, 10.9$ Hz), 3.79 (s, 3H), 2.45-2.60 (m, 2H), 2.27-2.29 (m, 1H), 1.23 (s, 3H), 1.14 (s, 3H), 0.98 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.7, 159.9, 137.6, 131.2, 127.3, 116.1, 113.5, 102.2, 83.8, 74.7, 55.2, 51.2, 41.5, 32.0, 21.3, 21.1, 7.9; IR (neat) 2973, 2936, 2838, 1703, 1616, 1518, 1249, 1119, 1035, 830 cm^{-1} ; HRMS calculated for $\text{C}_{19}\text{H}_{26}\text{O}_4$ $[\text{M} + \text{H}]^+$ 319.1909, found 319.1903; $[\alpha]_{\text{D}}^{20} -22.5^\circ$ (c 0.75, CHCl_3).

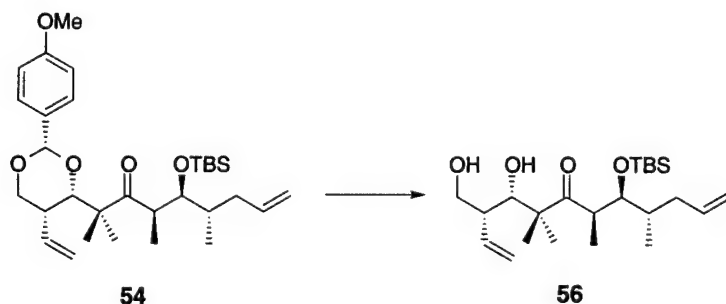
Preparation of **53**:



To a solution of diisopropylamine (197 μL , 1.40 mmol) in THF (2.6 mL) at 0°C was added $n\text{-BuLi}$ (602 μL , 2.31 M solution in THF, 1.39 mmol) dropwise. The solution was allowed to stir at this temperature for ten minutes before cooling to -78°C . To the LDA solution was then added a solution of ethyl ketone **52** (402 mg, 1.26 mmol) in THF (1.23 mL) dropwise and the resulting solution allowed to stir at this temperature for one hour. To the enolate solution was then added a solution of **42** (233 mg, 1.39 mmol) in THF (1.12 mL) dropwise. The reaction was allowed to continue at -78°C for ten minutes at which time an additional portion of aldehyde **42** (50 mg, 0.510 mmol) was added and the reaction allowed to continue stirring for ten minutes before being quenched by the addition of a saturated aqueous solution of NH_4Cl . The reaction mixture was then allowed to warm to room temperature and was diluted with water and the aqueous layer extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate followed by brine, dried (Na_2SO_4), concentrated *in vacuo*, and the resulting residue purified by flash column chromatography using a gradient of 7% to 10% ethyl acetate-petroleum ether to give the desired aldol adduct **53** (423 mg major diastereomer, 79%) in 59% diastereomeric excess: ^1H NMR (500 MHz, CDCl_3) δ 7.36 (d, 2H, $J = 8.7$ Hz), 6.85 (d, 2H, 8.7 Hz), 6.42 (ddd, 1H, $J = 10.2, 10.2, 17.2$ Hz), 5.65 (dddd, 1H, $J = 6.2, 8.3, 10.5, 16.7$ Hz), 5.46 (s, 1H), 5.12-5.13 (m, 1H), 5.10 (dd, 1H, $J = 1.7, 11.3$ Hz), 4.92-4.96 (m, 2H), 4.13 (dd, 1H, $J = 2.4, 11.0$ Hz), 4.10 (d, 1H, $J = 2.0$ Hz), 4.00 (dd, 1H, $J = 1.4, 11.0$ Hz), 3.75 (s, 3H), 3.50 (d, 1H, $J = 1.2$ Hz), 3.26 (d, 1H, $J = 9.2$ Hz), 3.20 (dq, 1H, $J = 1.4, 6.9$ Hz), 2.38-2.43 (m, 1H), 2.30-2.32 (m, 1H), 1.69 (dt, 1H, $J = 8.6, 13.7$ Hz), 1.46-1.55 (m, 1H), 1.30 (s, 3H), 1.13 (s, 3H), 0.97 (d, 3H, $J = 7.0$ Hz), 0.56 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 222.6, 160.0, 137.8, 137.0, 130.8, 127.4, 116.0, 115.9, 113.5, 102.3, 83.7, 74.9, 74.0, 55.1, 52.2, 41.4, 40.7, 37.1, 34.9, 20.8, 19.9, 14.5, 9.6; IR (neat) 3496, 3073, 2969, 1683, 1638, 1616, 1518, 1249, 1119, 995 cm^{-1} ; HRMS calculated for $\text{C}_{25}\text{H}_{36}\text{O}_5$ $[\text{M} + \text{Na}]^+$ 439.2460, found 439.2466; $[\alpha]_{\text{D}}^{20} -10.3^\circ$ (c 1.0, CHCl_3).

Preparation of **54**:

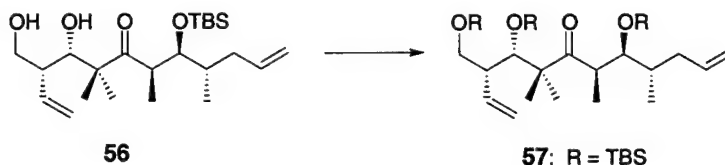
To a solution of aldol adduct **53** (193 mg, 0.464 mmol) in methylene chloride (2.3 mL) at -78°C was added 2,6-lutidine (254 μL , 2.18 mmol) followed by TBSOTf (224 μL , 0.974 mmol) and the reaction allowed to continue stirring at this temperature for 30 minutes before gradually warming to room temperature and continuing for two and one half hours. The reaction mixture was then extracted between aqueous pH 7 phosphate buffer and diethyl ether. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using 5% ethyl acetate-petroleum ether to give the desired TBS ether **54** (214 mg, 78%): ^1H NMR (500 MHz, CDCl_3) δ 7.35 (d, 2H, $J = 8.7$ Hz), 6.85 (d, 2H, 8.8 Hz), 6.46 (ddd, 1H, $J = 10.2, 10.2, 17.4$ Hz), 5.50 (s, 1H), 5.41-5.48 (m, 1H), 5.11 (dd, 1H, $J = 1.8, 10.3$ Hz), 5.07 (dd, 1H, $J = 1.8, 17.4$ Hz), 4.82-4.88 (m, 2H), 4.34 (d, 1H, $J = 2.0$ Hz), 4.18 (dd, 1H, $J = 2.4, 10.9$ Hz), 4.00 (dd, 1H, $J = 1.4, 10.9$ Hz), 3.80 (dd, 1H, $J = 1.7, 7.9$ Hz), 3.77 (s, 3H), 3.18 (dq, 1H, $J = 7.0, 7.0$ Hz), 2.29-2.32 (m, 1H), 2.06-2.11 (m, 1H), 1.67-1.73 (m, 1H), 1.31-1.35 (m, 1H), 1.28 (s, 3H), 1.15 (s, 3H), 1.03 (d, 3H, $J = 6.9$ Hz), 0.89 (s, 9H), 0.78 (d, 3H, $J = 6.9$ Hz), 0.047 (s, 3H), 0.039 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.6, 160.0, 138.5, 137.9, 131.1, 127.4, 115.6, 115.3, 113.5, 102.3, 82.6, 77.6, 75.2, 55.2, 52.1, 44.6, 41.8, 41.6, 38.0, 35.2, 26.2, 21.2, 21.0, 18.5, 17.8, 16.5, -3.6, -3.7; IR (neat) 2957, 2933, 1855, 1694, 1616, 1517, 1461, 1250, 1119 cm^{-1} ; HRMS calculated for $\text{C}_{31}\text{H}_{50}\text{O}_5\text{Si}$ $[\text{M} + \text{H}]^+$ 531.3506, found 531.3484; $[\alpha]_{\text{D}}^{20} -20.1^{\circ}$ (c 1.0, CHCl_3).

Preparation of **56**:

p-methoxybenzylidene acetal **54** (56 mg, 0.106 mmol) was dissolved in 80% acetic acid (5 mL) and the reaction allowed to stir at room temperature overnight. The reaction was quenched by the portionwise addition of solid sodium bicarbonate (until frothing ceased). The reaction mixture was then further diluted with water and extracted with dichloromethane. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 10% to 30% ethyl acetate-petroleum ether to give the desired diol **56** (34 mg, 78%): ^1H NMR (500 MHz, CDCl_3) δ 6.02 (ddd, 1H, $J = 10.2, 10.2, 17.3$ Hz), 5.70 (dddd, 1H, $J = 6.7, 6.7, 10.2, 16.9$ Hz), 5.17 (d, 1H, $J = 10.2$ Hz), 5.10 (d, 1H, $J = 17.4$ Hz), 4.97 (d, 1H, $J = 17.1$ Hz), 4.96 (d, 1H, $J = 10.0$ Hz), 3.96 (d, 1H, $J = 4.5$

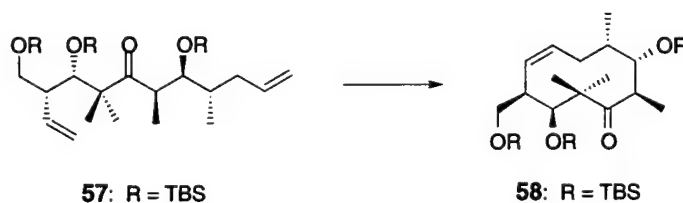
Hz), 3.80 (d, 1H, $J = 7.2$ Hz), 3.67-3.69 (m, 2H), 3.40 (d, 1H, $J = 4.7$ Hz), 3.13 (dq, 1H, $J = 6.7, 6.7$ Hz), 2.35-2.39 (m, 1H), 2.17-2.20 (m, 1H), 2.09 (m, 1H), 1.79-1.85 (m, 1H), 1.38-1.40 (m, 1H), 1.21 (s, 3H), 1.19 (s, 3H), 1.08 (d, 3H, $J = 6.9$ Hz), 0.90 (s, 9H), 0.89-0.90 (m, 3H), 0.074 (s, 3H), 0.064 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 221.8, 137.6, 136.4, 117.8, 115.8, 77.4, 76.4, 66.7, 52.2, 47.9, 44.9, 38.3, 35.3, 26.2, 22.3, 20.2, 18.6, 17.8, 16.6, -3.6, -3.7; IR (neat) 3427, 3074, 1685, 1639, 1472, 1253, 994 cm^{-1} ; HRMS calculated for $\text{C}_{23}\text{H}_{44}\text{O}_4\text{Si}$ $[\text{M} + \text{Na}]^+$ 435.2907, found 435.2919; $[\alpha]_{\text{D}}^{20}$ -18.0° (c 0.95, CHCl_3).

Preparation of **57**:



To a solution of diol **56** (100 mg, 0.243 mmol) in methylene chloride (1.2 mL) at -78 °C was added 2,6-lutidine (267 μL , 2.28 mmol) followed by TBSOTf (234 μL , 1.02 mmol) dropwise. The reaction was allowed to continue stirring with gradual warming to room temperature while monitoring by TLC. After approximately four hours at room temperature TLC analysis showed only one major spot corresponding to disilylation. The reaction mixture was extracted between aqueous pH 7 phosphate buffer and ethyl acetate. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using 1% ethyl acetate-petroleum ether to give the desired tri-TBS ether **57** (152 mg, 98%): ^1H NMR (500 MHz, CDCl_3) δ 5.89 (ddd, 1H, $J = 10.0, 10.0, 17.7$ Hz), 5.67-5.75 (m, 1H), 4.93-5.04 (m, 4H), 4.17 (s, 1H), 3.83 (dd, 1H, $J = 1.6, 7.5$ Hz), 3.53 (dd, 1H, $J = 7.6, 9.8$ Hz), 3.35 (dd, 1H, $J = 8.2, 9.5$ Hz), 3.10 (dq, 1H, $J = 7.0, 7.0$ Hz), 2.13-2.22 (m, 2H), 1.79-1.86 (m, 1H), 1.39-1.43 (m, 1H), 1.21 (s, 3H), 1.05 (d, 3H, $J = 6.9$ Hz), 1.03 (s, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89-0.91 (m, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.068 (s, 6H), 0.041 (s, 3H), 0.016 (s, 3H), 0.0057 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.2, 137.8, 136.8, 116.7, 115.6, 77.4, 74.4, 65.4, 54.6, 50.1, 45.3, 38.1, 35.2, 26.4, 26.3, 29.9, 25.9, 19.1, 18.8, 18.6, 18.3, 17.9, 15.5, -3.5, -3.6, -3.7, -5.2, -5.3; IR (neat) 1694, 1640, 1472, 1254, 1102, 836 cm^{-1} ; HRMS calculated for $\text{C}_{35}\text{H}_{72}\text{O}_4\text{Si}_3$ $[\text{M} + \text{Na}]^+$ 663.4636, found 663.4640; $[\alpha]_{\text{D}}^{20}$ -14.2° (c 1.0, CHCl_3).

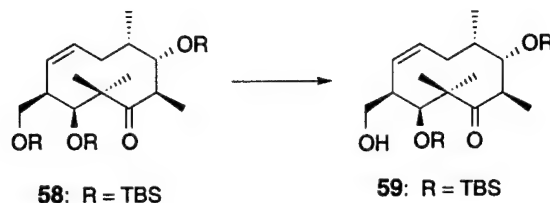
Preparation of **58**:



To a solution of tri-TBS ether **57** (70 mg, 0.109 mmol) in methylene chloride (515 mL, 0.2 mM) was added Grubbs' catalyst (27 mg, 0.0328 mmol). The resulting purple solution was then vigorously degassed before heating to reflux and continuing at this temperature for three days. The reaction was then cooled and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography using 1% diethyl ether-petroleum ether to give the desired *cis*-cycloundecene **58** (62 mg, 93%): ^1H NMR (500 MHz, CDCl_3) δ 5.34 (ddd, 1H, $J = 4.2, 11.6, 11.6$ Hz), 5.20 (dd, 1H, $J = 10.6, 10.6$ Hz), 3.98 (dd, 1H, $J = 3.7, 3.7$ Hz), 3.72 (s, 1H), 3.44 (dd, 1H, $J = 9.6, 9.6$ Hz), 3.28 (dd, 1H, $J = 6.0, 9.7$ Hz), 2.99, 3.07 (m, 2H), 2.01-2.08 (m, 1H), 1.90-1.94 (m, 1H), 1.80-1.86 (m, 1H), 1.34 (s, 3H), 1.11 (s, 3H), 0.93 (d, 3H, $J = 6.5$ Hz), 0.94 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87-0.89 (m, 3H), 0.13 (s, 3H),

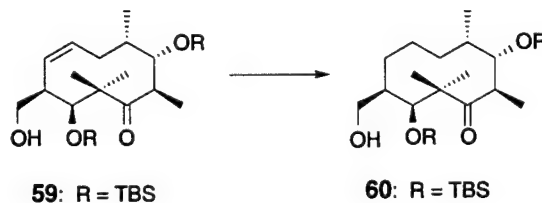
0.075 (s, 3H), 0.051 (s, 3H), 0.038 (s, 3H), 0.033 (s, 6H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 216.3, 129.0, 127.5, 79.4, 71.0, 64.7, 51.7, 41.1, 40.5, 39.4, 32.3, 27.0, 26.2, 26.0, 25.9, 23.6, 18.7, 18.2, 18.2, 15.8, 13.8, -3.1, -4.0, -4.5, -4.9, -5.2, -5.3; IR (neat) 1701, 1472, 1255, 1110, 838, 774 cm^{-1} ; HRMS calculated for $\text{C}_{33}\text{H}_{68}\text{O}_4\text{Si}_3$ $[\text{M} + \text{H}]^+$ 613.4504, found 613.4490; $[\alpha]_{\text{D}}^{20}$ -0.9° (c 1.0, CHCl_3).

Preparation of **59**:



To a solution of tri-TBS ether **58** (60 mg, 0.098 mmol) in methanol (0.9 mL) and methylene chloride (0.3 mL) at room temperature was added PpTS (cat.) and the reaction allowed to continue stirring at this temperature for approximately twenty hours. The reaction mixture was then extracted between aqueous pH 7 phosphate buffer and ethyl acetate and the combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 1% to 30% ethyl acetate-petroleum ether to provide recovered starting tri-TBS ether (26 mg) as well as the desired primary alcohol **59** (20 mg, 41%; 72% based on recovered starting material): ^1H NMR (500 MHz, CDCl_3) δ 5.53 (ddd, 1H, $J = 4.3, 11.6, 11.6$ Hz), 5.26 (dd, 1H, $J = 10.9, 10.9$ Hz), 3.98 (dd, 1H, $J = 3.7, 3.7$ Hz), 3.41-3.51 (m, 3H), 3.13 (dd, 1H, $J = 8.7, 17.4$ Hz), 3.06 (dq, 1H, $J = 3.1, 7.0$ Hz), 2.05-2.12 (m, 1H), 1.94-1.96 (m, 1H), 1.82-1.88 (m, 1H), 1.37 (s, 3H), 1.10 (s, 3H), 0.95 (d, 3H, $J = 7.3$ Hz), 0.93 (s, 9H), 0.88 (s, 9H), 0.87-0.88 (m, 3H), 0.13 (s, 3H), 0.080 (s, 3H), 0.050 (s, 3H), 0.042 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.9, 131.5, 127.4, 80.3, 71.2, 65.3, 51.9, 41.6, 40.8, 39.4, 32.3, 26.6, 26.2, 26.0, 23.5, 18.6, 18.2, 16.0, 13.8, -3.2, -3.9, -4.5, -4.9; IR (neat) 3472, 1701, 1473, 1253, 1114, 837, 774 cm^{-1} ; HRMS calculated for $\text{C}_{27}\text{H}_{54}\text{O}_4\text{Si}_2$ $[\text{M} + \text{Na}]^+$ 521.3458, found 521.3456; $[\alpha]_{\text{D}}^{20}$ $+15.7^\circ$ (c 0.95, CHCl_3).

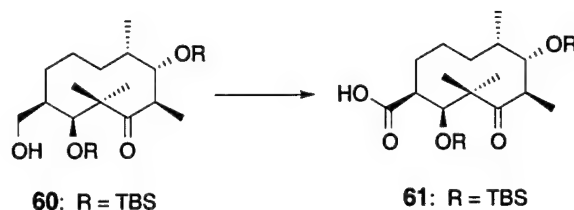
Preparation of **60**:



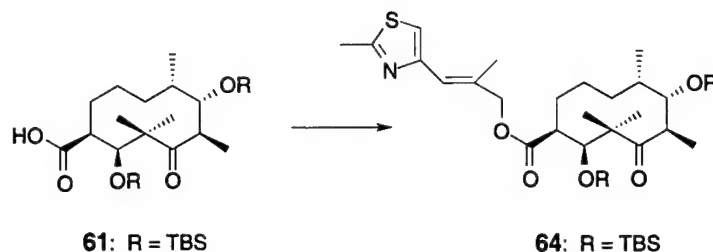
To a solution of cycloundecene **59** (31 mg, 0.0622 mmol) in ethanol (5 mL) was added platinum oxide (approx. 3 mg, 0.0132 mmol) and the resulting heterogeneous reaction mixture subjected to 4 atm. hydrogen gas with shaking for 24 hours. The reaction mixture was then filtered through a pad of celite, washing liberally with ethyl acetate to provide the desired cycloundecane **60** (31 mg, 100%): ^1H NMR (500 MHz, CDCl_3) δ 3.85 (d, 1H, $J = 5.8$ Hz), 3.60 (s, 1H), 3.47-3.50 (m, 1H), 3.42-3.43 (m, 1H), 3.14 (dq, 1H, $J = 6.7, 6.7$ Hz), 2.02-2.03 (m, 1H), 1.72 (m, 1H), 1.52-1.59 (m, 4H), 1.34 (s, 3H), 1.22-1.31 (m, 3H), 1.13 (s, 3H), 1.08 (d, 3H, $J = 6.8$ Hz), 0.94 (s, 9H), 0.88 (s, 9H), 0.86-0.88 (m, 3H), 0.076 (s, 3H), 0.069 (s, 3H), 0.058 (s, 3H), 0.011 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 218.2, 79.5, 79.0, 65.6, 52.3, 39.0, 34.1, 27.3, 27.0, 26.2, 26.1, 26.0, 23.7, 23.2, 22.3, 18.7, 18.5, 18.3, 18.1, -3.1, -3.5, -3.6, -4.3; IR (neat)

3475, 1694, 1472, 1253, 1070, 1021, 836, 773 cm^{-1} ; HRMS calculated for $\text{C}_{27}\text{H}_{56}\text{O}_4\text{Si}_2$ $[\text{M} + \text{Na}]^+$ 523.3615, found 523.3622; $[\alpha]_{\text{D}}^{20}$ -21.6° (c 1.0, CHCl_3).

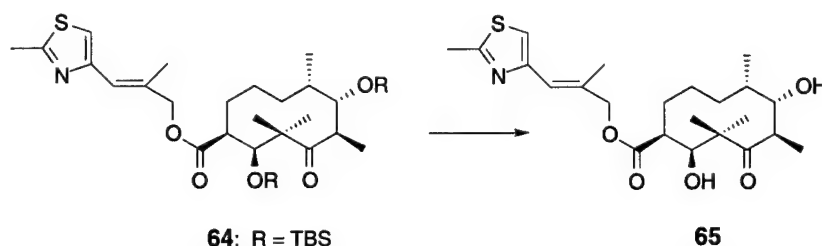
Preparation of **61**:



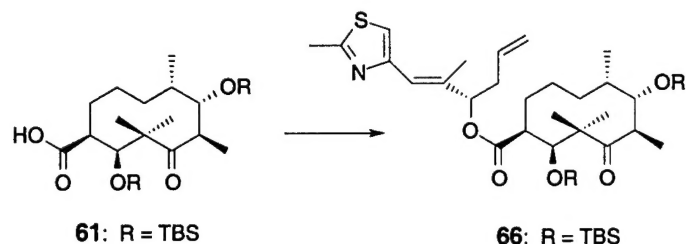
To a solution of primary alcohol **60** (31 mg, 0.0622 mmol) in acetone (0.5 mL) at 0°C was added Jones reagent dropwise (149 μL , 1.0 M, 0.149 mmol) and the reaction allowed to continue at this temperature for approximately four hours before storing at -5°C overnight. The reaction mixture was then extracted between water and ethyl acetate and the combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 10% to 20% ethyl acetate-petroleum ether to give the desired carboxylic acid **61** (20 mg, 62%): ^1H NMR (500 MHz, CDCl_3) δ 3.98 (br s, 1H), 3.85 (d, 1H, $J = 6.0$ Hz), 3.10-3.13 (m, 1H), 2.87 (m, 1H), 1.50-1.64 (m, 6H), 1.43-1.46 (m, 1H), 1.38 (s, 3H), 1.15 (s, 3H), 1.08 (d, 3H, $J = 6.6$ Hz), 0.93 (s, 9H), 0.89 (s, 9H), 0.86-0.89 (m, 3H), 0.071 (s, 9H), -0.047 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 217.1, 181.6, 79.2, 78.8, 52.6, 47.3, 42.1, 33.7, 27.0, 26.2, 25.9, 23.0, 22.9, 22.3, 18.5, 18.4, 18.2, 18.0, -3.5, -3.7, -3.9, -4.9; IR (neat) 2600-3300, 1699, 1472, 1253, 835, 774 cm^{-1} ; HRMS calculated for $\text{C}_{27}\text{H}_{54}\text{O}_5\text{Si}_2$ $[\text{M} + \text{Na}]^+$ 537.3408, found 537.3425; $[\alpha]_{\text{D}}^{20}$ -20.7° (c 0.55, CHCl_3).

Preparation of **64**:

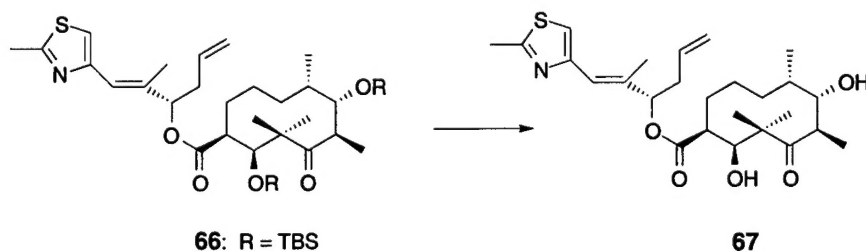
To a solution of acid **61** (20 mg, 0.0389 mmol) in methylene chloride (0.4 mL) at room temperature was added DCC (10 mg, 0.0506 mmol) followed by DMAP (6 mg, 0.0506 mmol). To the reaction mixture was then added a solution of thiazole alcohol **63** (8 mg, 0.0467 mmol) in methylene chloride (0.4 mL) and the reaction allowed to continue stirring for three hours. The mixture was then filtered through celite, washing liberally with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using a gradient of 2% to 5% ethyl acetate-petroleum ether to give the desired ester **64** (20 mg, 77%): ^1H NMR (500 MHz, CDCl_3) δ 6.95 (s, 1H), 6.50 (s, 1H), 4.64 (s, 2H), 3.95 (d, 1H, $J = 1.8$ Hz), 3.85 (d, 1H, $J = 7.2$ Hz), 3.13 (dq, 1H, $J = 6.9, 6.9$ Hz), 2.90 (d, 1H, $J = 8.4$ Hz), 2.70 (s, 3H), 2.10 (s, 3H), 1.43-1.68 (m, 7H), 1.38 (s, 3H), 1.15 (s, 3H), 1.06 (d, 3H, $J = 6.8$ Hz), 0.92 (s, 9H), 0.88 (s, 9H), 0.87-0.92 (m, 3H), 0.064 (s, 3H), 0.060 (s, 3H), 0.047 (s, 3H), -0.076 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 217.1, 175.6, 164.8, 152.4, 134.1, 121.6, 116.5, 79.4, 78.9, 70.6, 52.6, 47.3, 41.9, 34.1, 27.3, 26.2, 26.1, 25.9, 22.9, 22.5, 22.3, 19.2, 18.5, 18.4, 18.2, 17.9, 16.2, -3.5, -3.7, -3.9, -5.0; IR (neat) 1733, 1694, 1462, 1252, 835, 774 cm^{-1} ; HRMS calculated for $\text{C}_{35}\text{H}_{63}\text{NO}_5\text{SSi}_2$ $[\text{M} + \text{H}]^+$ 666.4044, found 666.4069; $[\alpha]_{\text{D}}^{20}$ -17.5° (c 0.4, CHCl_3).

Preparation of **65**:

To a solution of di-TBS ether **64** (10 mg, 0.015 mmol) in methylene chloride (0.5 mL) at 0 °C was added trifluoroacetic acid (0.2 mL) and the reaction stored at -5 °C for twenty hours before quenching by pouring the reaction solution into a cold saturated solution of aqueous sodium bicarbonate and extracting with chloroform. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the resulting residue purified by flash column chromatography using a gradient of 20% to 50% ethyl acetate-petroleum ether to provide the desired diol **65** (4 mg, 61%): ^1H NMR (500 MHz, CDCl_3) δ 6.94 (s, 1H), 6.48 (s, 1H), 4.66 (d, 1H, $J = 21.9$ Hz), 4.63 (d, 1H, $J = 21.9$ Hz), 3.91 (d, 1H, $J = 9.1$ Hz), 3.81 (d, 1H, $J = 9.6$ Hz), 3.67 (dd, 1H, $J = 2.4, 8.7$ Hz), 3.19 (dq, 1H, $J = 6.9, 8.6$ Hz), 2.69 (s, 3H), 2.58-2.59 (m, 1H), 2.07 (s, 3H), 1.93-1.96 (m, 1H), 1.79-1.84 (m, 1H), 1.44 (s, 3H), 1.37-1.44 (m, 4H), 1.35 (s, 3H), 1.28 (d, 3H, $J = 6.8$ Hz), 1.06-1.11 (m, 1H), 0.98 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 224.1, 174.9, 164.8, 152.4, 134.3, 121.3, 116.4, 80.8, 78.8, 70.5, 50.1, 48.7, 44.3, 30.2, 28.8, 25.7, 24.1, 23.0, 20.5, 19.2, 18.4, 18.1, 16.1; IR (neat) 3423, 1730, 1675, 1458, 1375, 1167, 979 cm^{-1} ; HRMS calculated for $\text{C}_{23}\text{H}_{35}\text{NO}_5\text{S}$ $[\text{M} + \text{H}]^+$ 438.2314, found 438.2315; $[\alpha]_{\text{D}}^{20}$ -15.0° (c 0.2, CHCl_3).

Preparation of **66**:

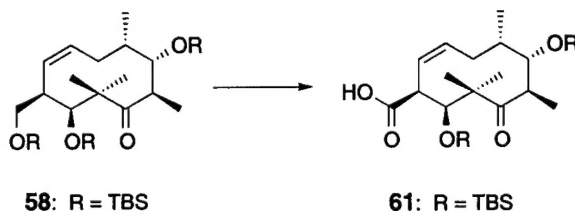
To a solution of acid **61** (5 mg, 0.00970 mmol) in methylene chloride (0.2 mL) at room temperature was added DCC (3 mg, 0.0126 mmol) followed by DMAP (2 mg, 0.0126 mmol). To the reaction mixture was then added a solution of thiazole alcohol **62** (2 mg, 0.0116 mmol) in methylene chloride (0.2 mL) and the reaction allowed to continue stirring for four. The mixture was then filtered through celite, washing liberally with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using a gradient of 2% to 5% ethyl acetate-petroleum ether to give the desired ester **66** (3 mg, 44%): ^1H NMR (500 MHz, CDCl_3) δ 6.92 (s, 1H), 6.48 (s, 1H), 5.73 (dddd, 1H, $J = 7.0, 7.0, 10.1, 17.0$ Hz), 5.33 (dd, 1H, $J = 6.6, 6.6$ Hz), 5.11 (dd, 1H, $J = 1.4, 17.1$ Hz), 5.06 (dd, 1H, $J = 1.4, 10.1$ Hz), 3.92 (d, 1H, $J = 2.1$ Hz), 3.84 (d, 1H, $J = 6.2$ Hz), 3.13 (dq, 1H, $J = 6.9$ Hz), 2.87 (d, 1H, $J = 7.7$ Hz), 2.69 (s, 3H), 2.44-2.56 (m, 2H), 2.08 (s, 3H), 1.65-1.71 (m, 1H), 1.55-1.58 (m, 3H), 1.42-1.49 (m, 2H), 1.37 (s, 3H), 1.14 (s, 3H), 1.06 (d, 3H, $J = 6.8$ Hz), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (d, 3H, $J = 6.9$ Hz), 0.85-0.89 (m, 1H), 0.062 (s, 3H), 0.060 (s, 3H), 0.043 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 217.0, 174.9, 164.7, 152.5, 136.8, 133.5, 121.2, 117.9, 116.5, 79.0, 78.8, 52.8, 47.5, 41.8, 37.8, 29.7, 27.3, 26.2, 25.9, 22.8, 22.4, 19.3, 18.5, 18.4, 18.3, 17.9, 14.6, 14.2, 14.0, -3.4, -3.6, -3.7, -5.0; IR (neat) 1729, 1694, 1472, 1252, 1113, 1018, 835, 774 cm^{-1} ; HRMS calculated for $\text{C}_{38}\text{H}_{67}\text{NO}_5\text{Si}_2$ $[\text{M} + \text{Na}]^+$ 728.4176, found 728.4191; $[\alpha]_{\text{D}}^{20}$ -22.7° (c 0.15, CHCl_3).

Preparation of **67**:

To a solution of di-TBS ether **66** (3 mg, 0.00430 mmol) in methylene chloride (0.3 mL) at 0 °C was added trifluoroacetic acid (0.1 mL) and the reaction stored at -5 °C for one day before quenching by pouring the reaction solution into a cold saturated solution of aqueous sodium bicarbonate and extracting with chloroform. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the resulting residue purified by flash column chromatography using a gradient of 20% to 40% ethyl acetate-petroleum ether to provide the desired diol **67** (2 mg, 98%): ^1H NMR (500 MHz, CDCl_3) δ 6.93 (s, 1H), 6.49 (s, 1H), 5.72 (dddd, 1H, $J = 7.0, 7.0, 9.8, 16.9$ Hz), 5.32 (dd, 1H, $J = 6.6, 6.6$ Hz), 5.08 (d, 1H, $J = 17.1$ Hz), 5.05 (d, 1H, $J = 10.2$ Hz), 3.86 (s, 1H), 3.66-3.68 (m, 2H), 3.18 (dq, 1H, $J = 6.8, 6.8$ Hz), 2.69 (s, 3H), 2.55 (d, 1H, $J = 6.6$ Hz), 2.45-2.52 (m, 2H), 2.06 (s, 3H), 1.90-1.93 (m, 1H), 1.77-1.80 (m, 1H), 1.22-1.52 (m, 5H), 1.44 (s, 3H), 1.33 (s, 3H), 1.28 (d, 3H, $J = 6.7$ Hz), 1.06-1.10 (m, 1H), 0.97 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 223.9, 174.2, 164.8, 133.4, 120.5, 117.8, 116.4, 80.8, 78.9, 78.4, 50.3, 48.6, 44.2, 37.7, 30.3, 28.6, 25.6, 24.0, 23.1, 20.5, 19.2, 18.3, 18.0, 14.8; IR (neat) 3456, 1733, 1667,

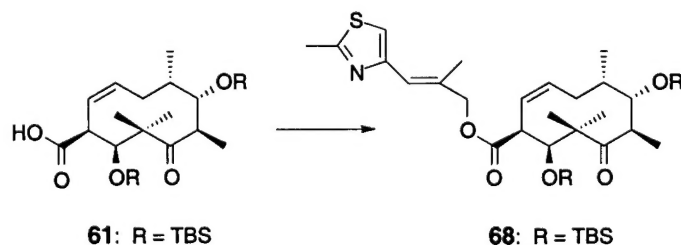
1456, 1169, 974 cm^{-1} ; HRMS calculated for $\text{C}_{26}\text{H}_{39}\text{NO}_5\text{S}$ $[\text{M} + \text{H}]^+$ 478.2627, found 478.2642; $[\alpha]_{\text{D}}^{20}$ -23.5 (c 0.10, CHCl_3).

Preparation of **61**:



To a solution of tri-TBS ether **58** (10 mg, 0.0163 mmol) in acetone (0.3 mL) at 0 °C was added Jones reagent (39 μL , 1.0 M, 0.0391 mmol) and the reaction allowed to continue at this temperature for approximately six hours. The reaction mixture was then extracted between water and ethyl acetate and the combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the residue purified by flash column chromatography using a gradient of 10% to 20% ethyl acetate-petroleum ether to give the desired carboxylic acid **61** (4 mg, 48%): ^1H NMR (500 MHz, CDCl_3) δ 5.55-5.60 (m, 1H), 5.49 (dd, 1H, J = 10.5, 10.5 Hz), 4.16 (s, 1H), 3.94 (dd, 1H, J = 4.0, 4.0 Hz), 3.89 (d, 1H, J = 9.8 Hz), 3.04 (dq, 1H, J = 4.0, 7.2 Hz), 1.99-2.06 (m, 2H), 1.87-1.90 (m, 1H), 1.38 (s, 3H), 1.15 (s, 3H), 0.97 (d, 3H, J = 7.2 Hz), 0.92 (s, 9H), 0.89 (d, 3H, J = 7.4 Hz), 0.88 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.050 (s, 3H), 0.024 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.3, 178.2, 131.4, 123.7, 80.3, 71.6, 52.1, 44.5, 41.4, 39.3, 31.9, 29.7, 26.0, 26.0, 23.3, 18.5, 18.2, 16.3, 14.2, -3.7, -4.4, -4.6, -4.8; IR (neat) 2425-3400, 1703, 1472, 1254, 1109, 836, 775 cm^{-1} ; HRMS calculated for $\text{C}_{27}\text{H}_{52}\text{O}_5\text{Si}_2$ $[\text{M} + \text{H}]^+$ 513.3431, found 513.3433; $[\alpha]_{\text{D}}^{20}$ -24.2 ° (c 0.6, CHCl_3).

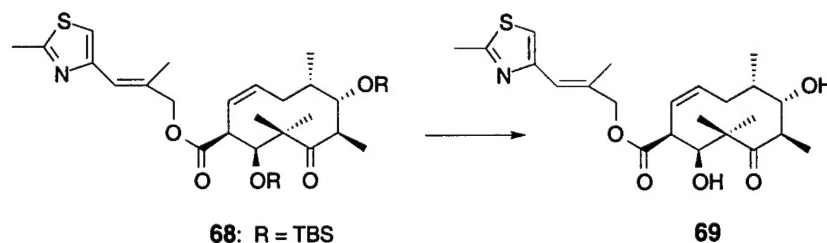
Preparation of **68**:



To a solution of acid **61** (12 mg, 0.0234 mmol) in methylene chloride (0.48 mL) at room temperature was added DCC (6 mg, 0.0304 mmol) followed by DMAP (4 mg, 0.0304 mmol). To the reaction mixture was then added a solution of thiazole alcohol **63** (5 mg, 0.0281 mmol) in methylene chloride (0.5 mL) and the reaction allowed to continue stirring for twenty hours. The mixture was then filtered through celite, washing liberally with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using 5% ethyl acetate-petroleum ether to give the desired ester **68** (11 mg, 71%): ^1H NMR (500 MHz, CDCl_3) δ 6.93 (s, 1H), 6.47 (s, 1H), 5.55 (ddd, 1H, J = 4.2, 11.2, 11.2 Hz), 5.46 (dd, 1H, J = 10.8, 10.8 Hz), 4.62 (d, 1H, J = 16.8 Hz), 4.60 (d, 1H, J = 16.8 Hz), 4.09 (d, 1H, J = 1.1 Hz), 3.92-3.96 (m, 2H), 3.06 (dq, 1H, J = 3.6, 7.0 Hz), 2.69 (s, 3H), 2.02-2.11 (m, 1H), 2.06 (s, 3H), 1.92-1.95 (m, 1H), 1.82-1.86 (m, 1H), 1.39 (s, 3H), 1.15 (s, 3H), 0.96 (d, 3H, J = 7.0 Hz), 0.91 (s, 9H), 0.88 (s, 9H), 0.87-0.88 (m, 3H), 0.12 (s, 3H), 0.079 (s, 3H), 0.042 (s, 3H), -0.0090 (s, 3H); ^{13}C NMR (125.7 MHz, CDCl_3) δ 215.3, 173.4, 164.8, 152.4, 134.0, 130.6, 124.3, 121.3, 116.4, 80.6, 71.8, 70.5, 52.1, 44.7, 41.4, 39.4, 31.8, 26.8, 26.0, 26.0, 23.0, 19.2, 18.5, 18.3, 16.1, 16.0, 14.4, -3.7, -4.4,

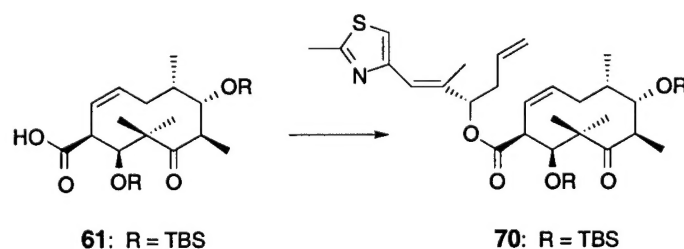
-4.6, -4.8; IR (neat) 1733, 1701, 1472, 1253, 1114, 835, 775 cm^{-1} ; HRMS calculated for $\text{C}_{35}\text{H}_{61}\text{NO}_5\text{SSi}_2$ $[\text{M} + \text{Na}]^+$ 686.3707, found 686.3698; $[\alpha]_{\text{D}}^{20}$ -32.5° (c 0.55, CHCl_3).

Preparation of **69**:



To a solution of di-TBS ether **68** (11 mg, 0.0166 mmol) in methylene chloride (0.5 mL) at 0 °C was added trifluoroacetic acid (0.2 mL) and the reaction stored at -5 °C for two days before quenching by pouring the reaction solution into a cold saturated solution of aqueous sodium bicarbonate and extracting with chloroform. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the resulting residue purified by flash column chromatography using a gradient of 30% to 50% ethyl acetate-petroleum ether to provide the desired diol **69** (3 mg, 42%): ^1H NMR (500 MHz, CDCl_3) δ 6.94 (s, 1H), 6.47 (s, 1H), 5.48-5.58 (m, 2H), 4.66 (d, 1H, J = 29.7 Hz), 4.63 (d, 1H, J = 29.7 Hz), 4.11 (br s, 1H), 3.91 (d, 1H, J = 10.5 Hz), 3.64 (d, 1H, J = 10.5 Hz), 3.62 (d, 1H, J = 9.1 Hz), 3.19 (dq, 1H, J = 7.2 Hz), 2.69 (s, 3H), 2.08-2.20 (m, 3H), 2.06 (s, 3H), 1.82-1.89 (m, 1H), 1.49 (s, 3H), 1.35 (s, 3H), 1.04 (d, 3H, J = 7.3 Hz), 0.92 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 223.3, 172.6, 164.8, 152.4, 134.2, 131.8, 123.7, 121.2, 116.4, 82.1, 70.5, 49.5, 44.9, 40.6, 38.2, 32.4, 29.7, 28.4, 23.2, 19.2, 16.0, 15.7, 13.0; IR (neat) 3462, 1729, 1676, 1452, 1235, 1165, 992 cm^{-1} ; HRMS calculated for $\text{C}_{23}\text{H}_{33}\text{NO}_5\text{S}$ $[\text{M} + \text{Na}]^+$ 458.1977, found 458.1974; $[\alpha]_{\text{D}}^{20}$ -43.0 (c 0.15, CHCl_3).

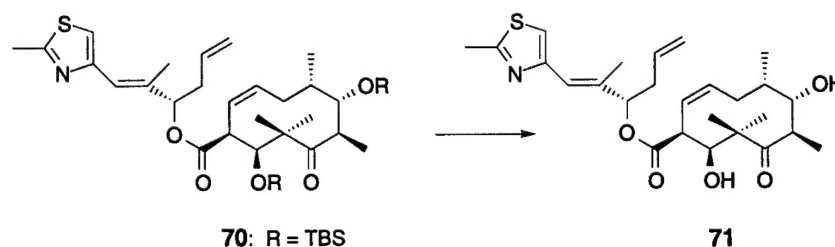
Preparation of **70**:



To a solution of acid **61** (5 mg, 0.00980 mmol) in methylene chloride (0.2 mL) at room temperature was added DCC (3 mg, 0.0127 mmol) followed by DMAP (2 mg, 0.0127 mmol). To the reaction mixture was then added a solution of thiazole alcohol **63** (2 mg, 0.0118 mmol) in methylene chloride (0.2 mL) and the reaction allowed to continue stirring for twenty hours. The mixture was then filtered through celite, washing liberally with methylene chloride, and the resulting solution concentrated *in vacuo* and purified by flash column chromatography using a gradient of 2% to 5% ethyl acetate-petroleum ether to give the desired ester **70** (4 mg, 58%). The desired product was contaminated with a small amount of impurity which was carried on to the next step. Due to this impurity, the ^{13}C spectrum was very difficult to interpret and has been omitted from the data reported for this compound. In addition, the region of the ^1H spectrum between 0.85 and 2.05 ppm has been assigned integration values as well as possible, however, these values cannot be known with absolute certainty: ^1H NMR (500 MHz, CDCl_3) δ 6.89 (s, 1H), 6.45 (s, 1H), 5.72 (dddd, 1H, J = 7.2, 7.2, 10.0, 17.2 Hz), 5.55 (ddd, 1H, J = 4.8, 11.0, 11.0 Hz), 5.40 (dd, 1H, J = 10.7, 10.7

Hz), 5.29 (dd, 1H, $J = 6.7, 6.7$ Hz), 5.10 (d, 1H, $J = 17.0$ Hz), 5.06 (dd, 1H, $J = 0.7, 10.9$ Hz), 4.06 (s, 1H), 3.96 (d, 1H, $J = 10.6$ Hz), 3.89 (dd, 1H, $J = 3.5, 3.5$ Hz), 3.06-3.08 (m, 1H), 2.68 (s, 3H), 2.43-2.52 (m, 2H), 2.05-2.15 (m, 1H), 2.03 (s, 3H), 1.60-1.90 (m, 3H), 1.37 (s, 3H), 1.13 (s, 3H), 0.97 (d, 3H, $J = 7.0$ Hz), 0.85-0.92 (m, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.12 (s, 3H), 0.070 (s, 3H), 0.033 (s, 3H), -0.036 (s, 3H); IR (neat) 1733, 1704, 1464, 1247, 1108, 832, 774 cm^{-1} ; HRMS calculated for $\text{C}_{38}\text{H}_{65}\text{NO}_5\text{SSi}_2$ [$\text{M} + \text{H}$] $^+$ 704.4200, found 704.4206; $[\alpha]_{\text{D}}^{20}$ -60.0° (c 0.2, CHCl_3).

Preparation of **71**:



To a solution of di-TBS ether **70** (4 mg, 0.00570 mmol) in methylene chloride (0.3 mL) at 0 °C was added trifluoroacetic acid (0.1 mL) and the reaction stored at -5 °C for one day before quenching by pouring the reaction solution into a cold saturated solution of aqueous sodium bicarbonate and extracting with chloroform. The combined organic extracts were dried (MgSO_4), concentrated *in vacuo* and the resulting residue purified by flash column chromatography using a gradient of 20% to 40% ethyl acetate-petroleum ether to provide the desired diol **71** (2.5 mg, 93%): ^1H NMR (500 MHz, CDCl_3) δ 6.92 (s, 1H), 6.48 (s, 1H), 5.71 (dddd, 1H, $J = 7.1, 7.1, 9.9, 17.0$ Hz), 5.46-5.56 (m, 2H), 5.30 (dd, 1H, $J = 6.7, 6.7$ Hz), 5.08 (d, 1H, $J = 17.1$ Hz), 5.04 (d, 1H, $J = 10.2$ Hz), 4.09-4.12 (m, 2H), 3.86 (d, 1H, $J = 10.5$ Hz), 3.55-3.60 (m, 2H), 3.18 (dq, 1H, $J = 7.2, 7.2$ Hz), 2.68 (s, 3H), 2.44-2.51 (m, 2H), 2.11-2.19 (m, 1H), 2.05-2.09 (m, 1H), 2.05 (s, 3H), 1.82-1.89 (m, 1H), 1.48 (s, 3H), 1.33 (s, 3H), 1.04 (d, 3H, $J = 7.3$ Hz), 0.92 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR (125.7 MHz, CDCl_3) δ 223.1, 171.9, 164.6, 152.6, 136.9, 133.4, 131.6, 123.7, 120.8, 117.8, 116.4, 82.0, 78.6, 70.5, 49.6, 45.0, 40.7, 38.2, 37.6, 32.3, 28.3, 23.1, 19.2, 15.6, 14.7, 13.0; IR (neat) 3468, 1729, 1678, 1453, 1167, 992 cm^{-1} ; HRMS calculated for $\text{C}_{26}\text{H}_{37}\text{NO}_5\text{S}$ [$\text{M} + \text{Na}$] $^+$ 498.2290, found 498.2294; $[\alpha]_{\text{D}}^{20}$ -41.6 (c 0.12, CHCl_3).

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